UNIVERSIDADE DE LISBOA
FACULDADE DE CIÊNCIAS
DEPARTAMENTO DE FÍSICA

Added value of combining VMAT with computer-selected patient-specific non-coplanar IMRT beams in radiotherapy for nasopharyngeal carcinoma and mediastinal lymphoma

Joana Marques da Silva Leitão

Mestrado Integrado em Engenharia Biomédica e Biofísica
Radiações em Diagnóstico e Terapia

Dissertação orientada por:
Ben Heijmen, Ph.D. Prof.
Nuno Matela, Ph.D.

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Resumo

Num organismo multicelular saudável, as células dividem-se, crescem, proliferam e morrem. Quando o sistema não está bem regulado, o crescimento descontrolado de células pode levar a um tumor. Doenças geradas pelo aumento exagerado do número células designam-se cancros.

Radioterapia (RT) é um tratamento que usa radiação para erradicar as células cancerígenas, poupando os tecidos saudáveis circundantes, tanto quanto possível. A radiação interage com as células depositando energia (dose). Em radioterapia de feixe externo (*external beam radiotherapy*, EBRT) o paciente está, normalmente, deitado numa mesa de tratamento, perto de um acelerador linear (*linear accelerator*, linac), que produz feixes de alta energia. Durante um tratamento de radioterapia a *gantry*, o braço do *linac* por onde são emitidos os feixes, roda em torno da mesa. Se só a *gantry* rodar, trata-se de um tratamento coplanar; se tanto a *gantry* como a mesa rodarem, o tratamento diz-se não-coplanar. Tratamentos não-coplanares permitem uma maior gama de posições, o que pode ser vantajoso para tumores mais complexos.

A radioterapia de intensidade modulada (*intensity-modulated radiotherapy*, IMRT) é uma técnica avançada em que o feixe o está dividido em pequenos feixes (*beamlets*), cuja intensidade é modulada individualmente. Nesta técnica, o dosimetrista define a distribuição de dose e o sistema calcula inversamente quais as melhores direções, intensidades e as formas dos segmentos dos *beamlets*. Num mesmo tratamento de IMRT podem ser usados vários feixes. Arcoterapia Volumétrica Modulada (*volumetric modulated arc therapy*, VMAT) é uma técnica de radioterapia em que a *gantry* roda à volta do paciente, durante a irradiação, formando um arco. VMAT pode ser usado com um arco parcial ou total, ou combinando múltiplos arcos. Tanto VMAT como IMRT com múltiplos feixes produzem resultados equivalentes na cobertura do volume alvo e salvaguarda dos órgãos em risco, no entanto os tratamentos com IMRT, quando são usados muitos feixes, são mais demorados.

No planeamento convencional para tratamentos de radioterapia, um dosimetrista deve modelar o plano equilibrando a cobertura do tumor e a proteção dos órgãos adjacentes. Este processo é demorado e depende da experiência do dosimetrista. Com o planeamento automático (*autoplanning*), o processo é otimizado e é alcançado o melhor plano possível. O Erasmus Medical Center (EMC), em Roterdão, Países Baixos, desenvolveu internamente um otimizador para a geração automatizada de planos de radioterapia chamado Erasmus-iCycle. O Erasmus-iCycle realiza otimização multicritério totalmente automatizada (*multi-criteria optimization*, MCO) dos perfis de intensidade e dos ângulos dos feixes de IMRT. O Erasmus-iCycle é conduzido por uma *wish-list* (”lista de desejos”), descrevendo restrições, requisitos que devem ser sempre cumpridos, e objetivos, metas de tratamento priorizadas que devem ser atendidas tanto quanto possível, sem violar as restrições. O resultado é um único plano Pareto-ótimo com balanços favoráveis entre a cobertura do volume alvo de planeamento (*planning target volume*, PTV), órgãos em risco (*organ at risk*, OAR) e tecidos saudáveis. O Erasmus-iCycle pode gerar planos para arranjos de feixe pré-determinados ou pode identificar o melhor arranjo de feixe para cada paciente - otimização do ângulo do feixe (*beam angle optimization*, BAO).

Nesta tese, VMAT+, uma nova técnica que combina VMAT coplanar com, no máximo, 5 feixes IMRT não-coplanares, otimizados por paciente, foi investigada para dois locais de tratamento: carcinoma nasofaríngeo (*nasopharyngeal carcinoma*, NPC) e linfoma mediastinal (*mediastinal lymphoma*, ML). O VMAT+ pretende conjugar os tempos de tratamento curtos do VMAT, com as vantagens da não-

coplanaridade dos feixes IMRT, criando planos de maior qualidade, com um aumento limitado no tempo de tratamento e melhores resultados para os órgãos. Para a geração de planos VMAT+, os feixes IMRT foram selecionados usando BAO.

Para cada um dos locais de tratamento, foram estudados pacientes previamente tratados. O protocolo clínico aplicado no EMC foi considerado para a criação de cada *wish-lists*. No caso do NPC, como a *wish-list* foi criada de raiz, foi necessário comparar os planos automaticamente gerados com os que foram aplicados clinicamente, tendo sido aplicado o mesmo arranjo de feixes em ambos os planos. Para analisar a influência do tempo de tratamento na seleção de tratamentos, foi pedido a 4 revisores que escolhessem qual o melhor e segundo melhor plano para cada paciente, considerando primeiro só a qualidade do plano e, depois, a qualidade do plano e o tempo de tratamento. Um tratamento VMAT demora cerca de 3 min e cada feixe adicionado demora mais 1.5 min. Por último, foi investigada a contribuição dos 5 feixes IMRT dos planos VMAT+5 para a dose média (D_{mean}) no PTV.

O NPC é um tumor de cabeça e pescoço, próximo a muitos órgãos saudáveis essenciais. A primeira parte deste estudo centrou-se na configuração de uma *wish-list* para o Erasmus-iCycle que gerasse planos com qualidade semelhante ou superior à dos planos aplicados clinicamente, para 11 pacientes. Posteriormente, excluíu-se um paciente que foi clinicamente tratado com VMAT não-coplanar e, para 10 pacientes, foram gerados, de forma totalmente automática, planos VMAT e VMAT+ com 1 a 5 feixes não coplanares. Considerando os OARs, os planos VMAT+, em geral, superaram o VMAT em termos de poupança dos órgãos. A qualidade dos planos aumentou com cada feixe adicionado, resultando em menor dose média para as glândulas parótidas e submandibulares, e para cavidade oral, menores volumes no paciente a receberem altas doses globais e menor dose máxima para a medula espinal. A poupança dos OAR depende do paciente, por exemplo para as glândulas parótidas todos os pacientes beneficiam de planos VMAT+, mas comparando o VMAT+5 com o VMAT a redução varia entre 1 e 5 Gy, de acordo com o paciente. Também para o esófago, as melhorias com VMAT+ são geralmente limitadas, mas para um paciente o VMAT+1 reduz em 8 Gy a dose média, comparado com plano VMAT. Na selecção de planos pelos revisores, os planos VMAT+ com maior número de feixes (> 2) foram considerados superiores aos restantes, mas para o VMAT+5 a alta qualidade não justifica o prolongado tempo de tratamento. Os planos VMAT+3 foram considerados, para a maioria dos pacientes, o melhor compromisso entre qualidade de plano-tempo de tratamento. Para os planos VMAT+5, os feixes adicionados contribuíram para a dose média no PTV.

Os linfomas são um grupo de doenças malignas sanguíneas que podem surgir em qualquer ponto do corpo, nomeadamente entre o pescoço e os pulmões - a área mediastinal. Para este estudo, além dos planos VMAT e VMAT+ foi também gerado um VMAT borboleta de arco completo (*full-arc butterfly VMAT*, FaB-VMAT), uma *class solution* já publicada, composta por um arco VMAT coplanar e um arco parcial não-coplanar. Vinte e cinco pacientes foram incluídos no estudo, resultando em 175 planos de tratamento gerados automaticamente. Todos os planos foram considerados clinicamente aceitáveis. Os planos VMAT+ e FaB-VMAT superaram os planos VMAT. Os feixes adicionados para os planos VMAT+ resultaram em D_{mean} para o coração e pulmões, e menores volumes a receberem 5 e 20 Gy, nos pulmões e no volume total do paciente. A poupança dos órgãos com VMAT+ variou consoante o paciente, por exemplo, para D_{mean} nos pulmões, todos os pacientes têm doses reduzidas em comparação com VMAT, mas a redução com VMAT+5 varia entre 0 a 1.5 Gy. O FaB-VMAT teve resultados semelhantes aos do VMAT+3, VMAT+4 ou VMAT+5. Quanto à relação qualidade de plano-tempo de tratamento, embora os planos VMAT com mais feixes (> 2) tivessem sido considerados superiores em termos de qualidade,

o tempo de tratamento foi considerado demasiado longo. Principalmente tendo em conta que, para a maioria dos pacientes, os planos FaB-VMAT eram semelhantes e o tempo de tratamento mais reduzido (5 min com o FaB-VMAT e mais 2.5, 4 e 5.5 min com o VMAT+3, VMAT+4 e VMAT+5, respetivamente). Para alguns pacientes os planos VMAT+3 e VMAT+4 ainda se justificavam, mas em geral, o FaB-VMAT produziu planos com grande qualidade e sem necessidade de optimização específica para cada paciente. Para os planos VMAT+5, os feixes adicionados contribuíram para a dose média no PTV.

Em conclusão, VMAT+, principalmente com mais de 2 feixes adicionados, melhorou a qualidade dos planos VMAT para ambos os locais de tratamento. O tempo de tratamento do VMAT+4 e do VMAT+5 foi considerado demasiado longo para a maioria dos pacientes. Para o carcinoma nasofaríngeo, VMAT+3 foi considerado o tratamento mais adequado; para o linfoma mediastinal, o VMAT+5 e o FaB-VMAT resultaram em planos de alta qualidade. No entanto, VMAT+ é altamente específico e o FaB-VMAT oferece um melhor compromisso entre qualidade do plano e tempo de tratamento.

Tanto para carcinoma nasofaríngeo como para o linfoma mediastinal, a melhor abordagem de tratamento pode depender da anatomia do paciente. Com planeamento automatizado, mais planos podem ser gerados por paciente, permitindo que seja selecionado o melhor plano.

Palavras-chave: VMAT, IMRT, Planeamento automático, Carcinoma nasofaríngeo, e Linfoma mediastinal.

Abstract

Radiotherapy treatments can be coplanar, where all treatment beams are in a plane perpendicular to the longitudinal patient axis, or non-coplanar, allowing also other beam directions. On regular linear accelerators (linacs), which produce the high energy beams used in radiotherapy treatments, non-coplanar treatment is realized using patient couch rotations in between delivery of beams. Non-coplanar treatment considers a wider range of candidate beams, with a potential of improving patient dose distributions. However, non-coplanar treatments may be time-consuming as it involves couch rotations that may require technicians entering the treatment room prior to delivery of each beam to rotate the couch.

In conventional manual planning for radiotherapy treatments, a dosimetrist has to steer the treatment planning system (TPS) to achieve a plan with adequate trade-offs between tumor coverage and protection of surrounding organs. This process is time-consuming and plan quality depends on the experience and allotted time of the dosimetrist. Automated planning (autoplanning) can optimize the planning process, resulting in high-quality plans, independent of the skills of planners. The Erasmus Medical Center (EMC), in Rotterdam, the Netherlands, has an in-house developed optimizer for automated multi-criteria plan generation called Erasmus-iCycle. Erasmus-iCycle performs fully automated multi-criteria optimization (MCO) of both beam intensity profiles and beam angles. Erasmus-iCycle is driven by a "wish-list", describing constraints, requirements that must always be met, and prioritized treatment objectives with goals that should be met as much as possible, without violating the constraints. The output is a single Pareto-optimal plan with clinically favorable balances between coverage of the planning target volume (PTV), organs at risk (OAR) and healthy tissues. Erasmus-iCycle can generate plans for given beam arrangements or can identify the best beam arrangement for each patient using beam angle optimization (BAO). In this thesis, Erasmus-iCycle was used to investigate the added value of VMAT+ compared to other treatment approaches for two treatment sites: nasopharyngeal carcinoma (NPC) and mediastinal lymphoma (ML).

VMAT+ is a specific approach for non-coplanar treatment in which coplanar volumetric modulated arc therapy (VMAT) is complemented with a few (<5) computer-optimized non-coplanar intensity-modulated (IMRT) beams. VMAT+ plans are generated using a coplanar VMAT as a base and adding non-coplanar beams consecutively, i.e. VMAT+1 is a coplanar VMAT combined with one patient-optimized IMRT beam, VMAT+2, a coplanar VMAT with the previously defined IMRT, plus another patient-optimized beam, selected as the best addition to the VMAT+1; and so on up to VMAT+5.

NPC is a head and neck tumor, near many critical healthy organs. The first part of this study focused on a configuration of Erasmus-iCycle such that similar or superior plan quality as in the clinically applied plans was achieved. Subsequently, for 10 patients, VMAT and VMAT+ plans with 1-5 non-coplanar beams (total of 60 plans), were generated fully automatically using Erasmus-iCycle. Considering the OARs, VMAT+ plans, on average, outperformed VMAT. Plan quality increased with added number of beams, with lower D_{mean} for the parotids, submandibular glands and oral cavity, lower volumes receiving high doses overall and lower maximum dose of the spinal cord. OAR-sparing was patient-specific, for example for the parotids, all patients gain from VMAT+ plans, but the gain with VMAT+5 compared to VMAT ranges from 1 to 5 Gy. Also for the esophagus, improvements with VMAT+ are usually limited, but for one patient VMAT+1 reduces esophagus D_{mean} by 8 Gy. Considering plan quality and treatment time delivery, VMAT+3 was found to be, for most patients, the best compromise.

For mediastinal lymphoma (ML) full-arc butterfly VMAT (FaB-VMAT), a published class solution made up of a coplanar VMAT arc and a non-coplanar partial-arc, was generated along with VMAT and VMAT+ plans. Twenty-five patients were included in the study, resulting in 175 plans. All 175 automatically generated treatment plans were clinically acceptable. VMAT+ and FaB-VMAT plans outperformed VMAT plans, but none of the VMAT+ was clearly superior to FaB-VMAT, nor the opposite was true. Added beams in VMAT+ resulted in lower D_{mean} doses for the heart and lungs, and lower $V_{5\,Gy}$ and $V_{20\,Gy}$ in the lungs and the patient. VMAT+ sparing was patient-specific, for example for lungs D_{mean}, all patients have reduced doses compared to VMAT, but the sparing with VMAT+5 varied from 1.5 to 0 Gy. FaB-VMAT had similar results to either VMAT+3, VMAT+4 or VMAT+5. FaB-VMAT has no-patient-specific beam arrangements which eliminated the planning time required for beam-angle selection in the VMAT+ technique and is a much faster treatment.

In conclusion, VMAT+ improved VMAT plan quality for both treatment sites. For nasopharyngeal carcinoma, VMAT+3 was found to be the most appropriate treatment; for mediastinal lymphoma, both VMAT+5 and FaB-VMAT resulted in high-quality plans. However, VMAT+ was highly patient-specific and FaB-VMAT offers the best compromise between high plan quality and treatment time.

Keywords: VMAT, IMRT, Automated planning, Nasopharyngeal carcinoma, and Mediastinal lymphoma

Table of Contents

List of Figures

List of Tables

List of Abbreviations

RT	Radiotherapy
EBRT	External Beam Radiotherapy
Linac	Linear Accelerator
3DCRT	Three Dimensional Conformal Radiotherapy
IMRT	Intensity Modulated Radiation Therapy
MLC	Multi-leaf Collimator
VMAT	Volumetric Modulated Arc Therapy
GTV	Gross Tumor Volume
CTV	Clinical Target Volume
PTV	Planning Target Volume
OAR	Organ at Risk
CT	Computed Tomography
TPS	Treatment Planning System
EMC	Erasmus Medical Center
MCO	Multi-criteria Optimization
BAO	Beam Angle Optimization
NPC	Nasopharyngeal Carcinoma
SMG	Submandibular Glands
SwM	Swallowing Muscles
NHL	Non-Hodgkin Lymphoma
HL	Hodgkin Lymphoma
ML	Mediastinal Lymphoma
FaB-VMAT	Full-arc Butterfly VMAT
VMAT+	Coplanar VMAT supplemented with less than or equal to 5 patient-optimized non-coplanar IMRT beams
PTV70	Primary tumor and pathological lymph nodes, for NPC patients
PTV54.25	Elective nodal areas, for NPC patients
cc	Cubic centimeters
$\mathbf{D_{mean}}$	Mean dose
$\mathbf{D_{0.03\ cc}}$	Dose in the 0.03 cc that receive the highest dose, for a given OAR
EUD	Equivalent Uniform Dose

LTCP	Logarithmic Tumor Control Probability
VMAT plans	Automatically generated NCP plans, with the same beam configuration as clinical plans
$\mathbf{VMAT_t}$	VMAT translated
ClinVMAT plans	Clinically applied plans, for NPC patients
$\mathbf{V_{95\%}}$	Volume receiving 95% of the prescribed dose
$\mathbf{V_{107\%}}$	Volume receiving 107% of the prescribed dose
CI	Conformity Index
$\mathbf{V_{10\ Gy}}$	Volume receiving 10 Gy
$\mathbf{V_{30\ Gy}}$	Volume receiving 30 Gy
$\mathbf{V_{50\ Gy}}$	Volume receiving 50 Gy
$\mathbf{V_{110\%}}$	Volume receiving 110% of the prescribed dose
$\mathbf{V_{<90\%}}$	Volume receiving less than 90% of the prescribed dose
$\mathbf{V_{5\ Gy}}$	Volume receiving 5 Gy
$\mathbf{V_{20\ Gy}}$	Volume receiving 20 Gy
NS	Non-statistically significant, p-value > 0.05

1 Basics of Radiotherapy

1.1 Cancer

Cancer refers to a group of diseases characterized by uncontrolled cell growth [13]. More than one hundred types of cancer exist, depending on the type of cell that is initially affected.

In a healthy multicellular organism, cells undergo division, growth and proliferation, under well regulated control. When a cell is too old or too damaged, it ceases to carry out its functions and dies. At the same time, cells undergo division and reproduction when needed, controlling the total number of active cells. A deviation from the overall well-regulated control can lead to a tumor. A tumor is called malignant if cells are able to spread or invade nearby tissues; if the tumor only grows locally, it is a benign tumor.

1.1.1 Cancer treatment

Cancer treatment depends on the type of cancer and the stage. The intent may be curative or palliative (to reduce symptom severity in terminal cases). Treatments may involve drug administration through the blood flow, as in chemo and hormonal therapy, or be directed to a specific area, through surgery or irradiation [14].

In this thesis, the main focus is on the use of irradiation for treatment, called radiotherapy.

1.2 Radiotherapy

Radiotherapy (RT) is a treatment that uses radiation to eradicate cancer cells. This modality is based on the destruction of the tumor using radiation while saving the surrounding healthy tissues as much as possible.

1.2.1 Physics of radiotherapy

Electromagnetic radiation can be divided in two main categories, ionizing or non-ionizing radiation, depending on its ability to ionize matter. In radiotherapy, ionizing radiation, such as x-ray photons, electrons, protons or heavy ions are used.

X-ray photons are used in most radiotherapy treatments. X-rays are produced sending accelerated electrons against a high atomic number material, such as a tungsten target in a radiotherapy machine. Depending on beam energy, photons may interact differently with matter, as described below.

Photon interactions

X-rays photons can interact with the matter by several different mechanisms. The probability of each interaction depends on the energy of the photon and the atomic number of the material that the photon is interacting with, as represented in figure 1.1.

In photon beam radiotherapy three principal interactions can be identified:

- **Photoelectric effect**, results in the transfer of the total energy of a photon to an inner electron of an atom of the absorbing medium;

- **Compton scattering**, part of the energy of the photon is transferred to an electron. This "Compton electron" is set into motion with a kinetic energy equal to the energy transferred by the incident photon, minus any binding energy that must be overcome in ejecting the electron from its atom;
- **Pair production**, occurs near the nucleus of an atom in the absorbing medium and results in complete disappearance of the photon and appearance of a pair of bosons, one negative (electron) and one positive (positron).

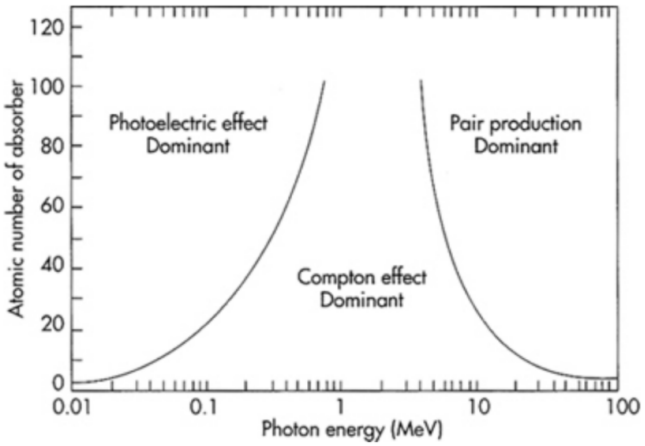


Figure 1.1: Regions of dominance of the three most occurring processes of interaction between photons and matter, as a function of the energy of the photon and atomic number of the absorber. From [1].

The Compton effect is the dominant interaction in a radiotherapy treatment effect, as most treatments are performed at energy levels between 1 and 15 MeV.

1.2.1.1 Radiation Dose

When a photon beam enters the patient, it interacts with tissues. The photon intensity is largest close to the point of entrance, resulting in a higher number of interactions with the medium. From these interactions, secondary particles, such as electrons, are created; these particles travel forward, adding to the ionization produced by the original photons. This phenomena causes the so called build-up region, resulting in the maximum absorbed occurring a bit inside the patient and not exactly at the surface, as in that region initial photon interactions and secondary particles sum up (see figure 1.2). After the build-up region, the photon beam intensity reduces with depth, resulting in less dose deeper in the patient body.

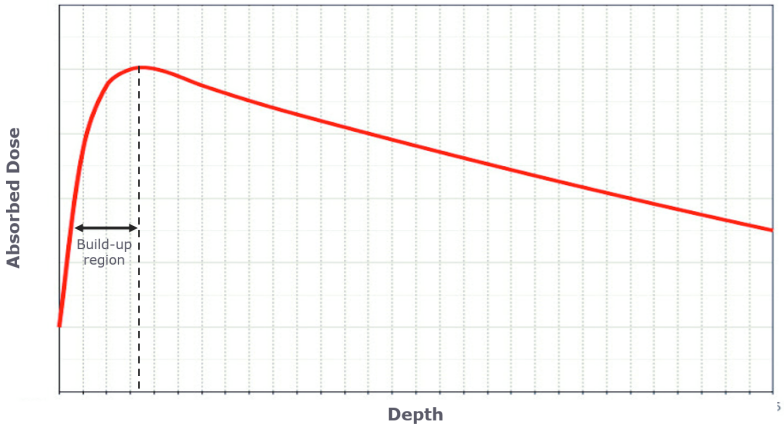


Figure 1.2: Schematic representation of absorbed dose and build-up as functions of depth. Adapted from [2].

The accumulated energy delivered by the photons and other particles is used to calculate the absorbed dose: the energy deposited by the ionizing radiation per unit of mass of material (J/Kg). Usually this parameter is presented in "gray" (Gy) where 1 Gy = 1 J/kg.

1.2.2 Techniques of radiotherapy

Considering the ionization source, there are two types of radiotherapy:

1. **Brachytherapy**: the source of radioactive material is inside or near the tumor;
2. **External beam radiotherapy (EBRT)**: high energy beams are produced externally, travelling through the patient, and directed at the tumor.

In this thesis, we will focus on EBRT.

1.3 External Beam Radiotherapy

In modern radiotherapy, the patient is usually laying down on a treatment couch, which is placed in the proximity of a linear accelerator (linac, figure 1.3) that produces narrow high energy beams. For example, x-rays beams are produced in interactions of energetic electrons with nuclei (*bremsstrahlung*) or electrons (characteristic photon) of high atomic number materials, such as a tungsten target. The beams are delivered by the gantry that is able to rotate 360 ^{o} around the moveable treatment couch [3].

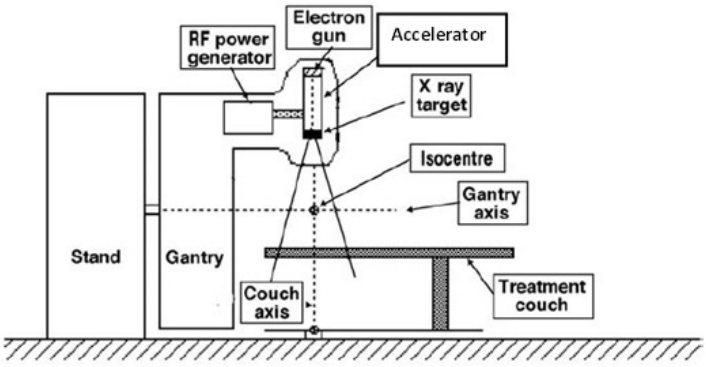
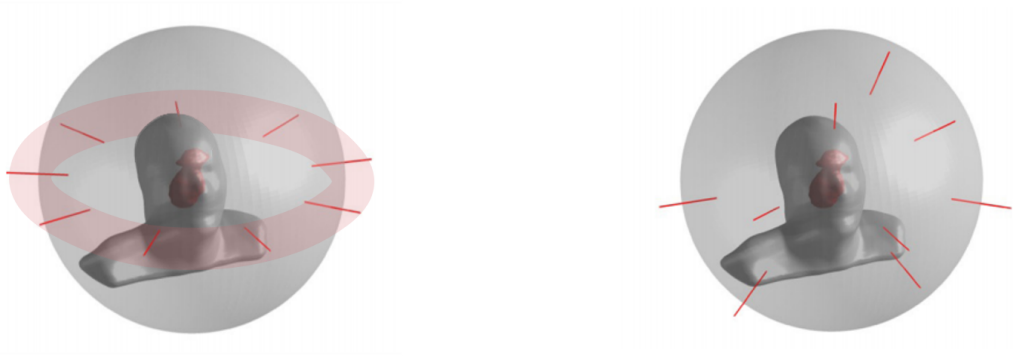


Figure 1.3: Schematic representation of a linear accelerator. Adapted from [3].

Radiotherapy treatments usually apply multiple beams. Using one single beam is suboptimal for deeper tumors, since it would give a higher dose near the entrance where healthy tissues are than at depth where the tumor lays (as explained in section 1.2.1). Combining multiple beams, that are focused at the location of the tumor, is needed to concentrate the dose in the target and spare tissues surrounding it [3].

Beams can be delivered from many angles by rotating the gantry and moving the treatment couch. The most common treatments use only gantry rotation, with fixed treatment couch. These are referred to as coplanar arrangements (figure 1.4a).

For complex target volumes, the couch can also be rotated, providing a wider range of beams created by moving the couch as well as the gantry. This results in non-coplanar beam arrangements with increased degrees of freedom (figure 1.4b), which allows to highly modulate the dose and can improve plan quality. However, non-coplanar treatments are more time-consuming than the coplanar ones as the radiotherapy technician may need to enter the room to rotate the couch and check the positioning [15].



(a) Coplanar **(b)** Non-Coplanar

Figure 1.4: Possible treatment geometries for a) coplanar and b) non-coplanar beam arrangements. In coplanar beam arrangements, all beams are in the same plane (marked by a red ellipse), only the gantry rotates; in non-coplanar beam arrangements, gantry and couch rotate. Adapted from [4]

1.3.1 Treatment modalities

In the last decades, progress was made in treatment planning and delivery. Treatment modalities have evolved to allow for a higher level of precision and accuracy in the delivery of radiation.

1.3.1.1 Conformal radiation therapy

In three dimensional conformal radiation therapy (3DCRT) the planner defines the beam directions and shapes in order to cover the target, usually consisting of big open field, encompassing the whole tumor, shaped with high atomic number material blocks. Beams definitions is performed in a trial-and-error process, until acceptable dose distribution is achieved [3].

1.3.1.2 Intensity-modulated radiation therapy

Intensity-modulated radiation therapy (IMRT) is an advanced form of radiotherapy, which uses intensity-modulated, non-uniform radiation beams during irradiation. This technique employs two main tools:

- **Modulation of the intensity**: IMRT does not use a big open field anymore, but divides the treatment beam into subfields (called segments) each with a different shape, intensity and position. This is done by shaping the subfields with a multi-leaf collimator (MLC, figure 1.5a).
- **Inverse planning:** contrary to direct planning, which works in defining the beam directions and intensity in order to cover the tumor, in inverse planning, the planner works in defining the dose distribution characteristics they want to achieve, and the system indirectly defines the beam directions, segment shapes and intensities needed to obtain it [16].

As a result, in a IMRT treatment, the dose distribution can be shaped to the tumor, as schematically represented by figure 1.5b, where each of the three IMRT beams has a different intensity profile (dose represented by the yellow curves), shaped according to the closest structure of interest (tumor or healthy organ).

The higher degree of freedom that IMRT offers represents one of the most important advances in radiotherapy, since it allows to highly shape the dose around the target, avoiding healthy structures next to it [17, 18].

(a) MLC **(b)** IMRT

Figure 1.5: Representation of a) a multi-leaf collimator and b) intensity modulation for three beams. In IMRT the subfields from each beam can have different intensities, which facilitates sparing of the organs surrounding the tumor (represented by a yellow curve, for each beam). This allows high coverage of the tumor and sparing of near-by organs. Adapted from [5].

In current IMRT treatments, beam geometry is defined by a template for each treatment site or selected by a planner based on previous experience, and adjusted for each patient in a trial-and-error procedure. In treatment planning, multiple structures and corresponding limits need to be considered, making it a very complex problem. The resulting plan quality depends on planner and clinical experience and may not be ideal for each patient. Selecting the optimal beam configuration for each patient may improve plan quality, through improved target coverage and organ sparing [19].

1.3.1.3 Volumetric modulated arc therapy

Volumetric modulated arc therapy (VMAT) is a radiation technique where the gantry rotates during irradiation, following an arc around the patient. VMAT can achieve highly modulated dose distributions with high target coverage and low healthy tissues irradiated. Multiple (full or partial) arcs can be combined to treat more complex volumes [18].

With VMAT, the possibility of dose delivery while rotating and adapting MLC positions, can lead to faster treatments, compared to conventional static field IMRT [20].

VMAT and IMRT with many beams produce equivalent results in terms of target volume coverage, dosimetric parameters, and dose conformity and homogeneity. However, using many IMRT beams increases treatment time.

1.4 Radiotherapy Treatment Planning

The aim for the treatment plan is to find the best compromise between irradiation of the target volume and sparing the healthy tissue surrounding the target [3]. As such, the tumor and organs near the tumor need to be identified.

1.4.1 Treatment Volume Definition

In planning, the following volumes of interest are defined:

- the **Gross Tumor Volume (GTV)** is visible and palpable tumor. It is determined by clinical examination or imaging techniques;
- the **Clinical Target Volume (CTV)** is the tissue volume that contains the GTV and subclinical malignant disease;

- the **Planning Target Volume (PTV)** surrounds the CTV with a margin to compensate for uncertainties because of organ motion, beam alignment and patient positioning;
- an **Organ at Risk (OAR)** might be damaged during irradiation and therefore the dose delivered needs to be controlled.

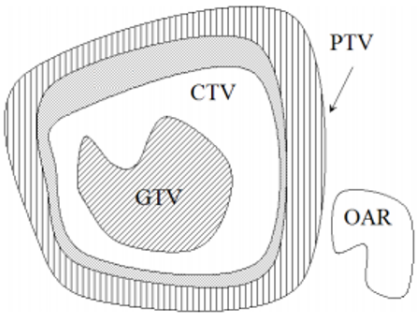


Figure 1.6: Volumes of interest: Gross tumor Volume (GTV), Clinical Target Volume (CTV) and Planning Target Volume (PTV) next to an organ at risk (OAR). From [3].

The target volumes (GTV, CTV and PTV) have to be adequately covered by a pre-defined dose. Surrounding OARs and healthy tissue must subsequently be spared as much as possible, by avoiding their irradiation [21].

1.5 Treatment plan generation

The quality of a radiotherapy treatment plan depends on, the modality of the treatment, where and how dose is delivered, the number of beams/arcs and their arrangements.

The radiotherapy workflow starts with CT acquisition. The images are studied and the relevant structures, both the target and the OARs (section 1.4), are identified and delineated in each slice of the CT (figure 1.7).

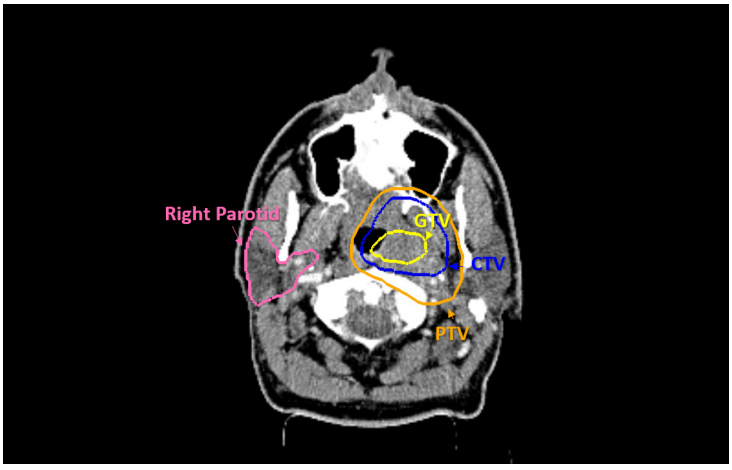


Figure 1.7: An example slice of a delineated CT. Right parotid is one of the OARs for this treatment.

For each treatment site, a team of physicians, medical physicists and radiotherapy technicians has defined a clinical protocol, consisting of the prescribed dose, fractionation scheme, dosimetrical requirements and RT technique. Then a treatment plan is generated using a treatment planning system (TPS).

1.5.1 Clinical IMRT/VMAT treatment plan generation

In the TPS, the planner has to create a plan for every patient treatment. They will use the patient CT with all target and OAR structure (section 1.4.1) as input for the TPS and define the number and arrangement of beams/arcs, usually chosen based on clinical experience for similar tumors.

Then the planner defines a list of cost functions to steer the TPS to fulfill clinical protocol and wishes. For every patient, the goal values of the cost functions are tuned in an iterative manner, in such a way that the optimizer finds a clinically desired trade-off between target coverage and OAR sparing.

This makes clinical treatment planning a time-consuming iterative procedure resulting in treatment plan quality that among other factors highly depends on experience, ambition and allotted time of the planner.

At the Erasmus Medical Center (EMC), the clinically used TPS is Monaco (Elekta AB, Stockholm, Sweden), a commercial clinical treatment planning system for IMRT and VMAT treatments.

2 Introduction to performed investigations

In this thesis, we performed plan generation, using automated planning, to investigate the benefit of non-coplanar IMRT beams in nasopharyngeal carcinoma and mediastinal lymphoma.

2.1 Automated treatment plan generation with Erasmus-iCycle

Erasmus-iCycle is the in-house developed TPS for automated multi-criteria plan generation [6]. Erasmus-iCycle performs fully automated multi-criteria optimization (MCO) of both beam intensity profiles and beam angles, explained more in detail below.

Compared to manual planning, Erasmus-iCycle does not require that the planner iteratively changes goal values in a template during each optimization. Automated planning with Erasmus-iCycle minimizes hands-on planning time and, with appropriate treatment site specific configuration ('wish-list', see below) generates high-quality plans [22]. Generated plans are Pareto-optimal, meaning that if an alternative plan is superior in one objective, it is less good in at least one other objective. Erasmus-iCycle is already successfully applied for head and neck [23], cervix [24], lungs [25], spinal metastases [26], prostate cancer [27, 28] and advanced gastric cancer [29].

2.1.1 Details of Erasmus-iCycle for plan generation

Erasmus-iCycle treatment planning performs a multi-criteria optimization, considering all competing requirements defined by the user.

The list of requirements are defined for each treatment site and are collected in a so called "wish-list", as in table 4.1.

In the wish-lists two types of requirements (wishes) can be defined:

- **Constraints**, requirements that are always respected and not optimized further;
- **Objectives**, prioritized treatment goals that should be met as much as possible without violation of constraints.

Optimization follows the priorities assigned to the objectives: high priority goals are attempted to be satisfied before lower priority goals, while strictly fulfilling the imposed constraints. Optimization goes through the wish-list two times. First, objectives are sequentially minimized to their goal values while respecting the constraints, starting with the highest prioritized objective; after each optimization, a constraint is added with as a limit the prescribed objective goal value or, in case it was not feasible to achieve the goal, the obtained value for that objective. This new constraint guarantees that during optimization for the lower priorities, the obtained result is not jeopardized. This means that the lower the priority, the more constraints are used. In the second phase, objectives that were optimized to their goal value or lower in the first phase, are optimized again, following their ascribed priority and respecting all the constraints. The output is a single Pareto-optimal plan with clinically favorable balances between all requirements in the wish-list.

Wish-list development starts with a first, (educated) guess wish-list based on the clinical protocol for the specific site. This wish-list is then used in an iterative process consisting of 1) plan generation for a (small) set of patients; 2) evaluation of automated plans and comparison with the clinically applied plans; 3) tuning of the wish-list; 4) stepping back to 1). In each iteration the wish-list is improved to maximally

reflect the physician's wishes and/or improve dose distributions. This process is stopped when no more improvement seems possible [22].

Mimicking the clinical results ensures that automated plans comply with clinical planning aims and trade-offs, and the iterative process of wish-list generation has an intrinsic drive to surpass clinical plan quality [30, 23, 24].

2.1.2 Beam angle optimization

Erasmus-iCycle can generate plans for given IMRT beam arrangements or can perform beam angle optimization (BAO). BAO identifies the best beam arrangement for each patient anatomy and treatment, chosen from a given candidate beam set. Beam candidate input can be defined by the user, including all the clinical limitations (e.g. regions of collisions between the gantry and the patient), if desired, and can be restricted to only consider coplanar arrangements or also allow non-coplanar candidates, for example (figure 2.1).

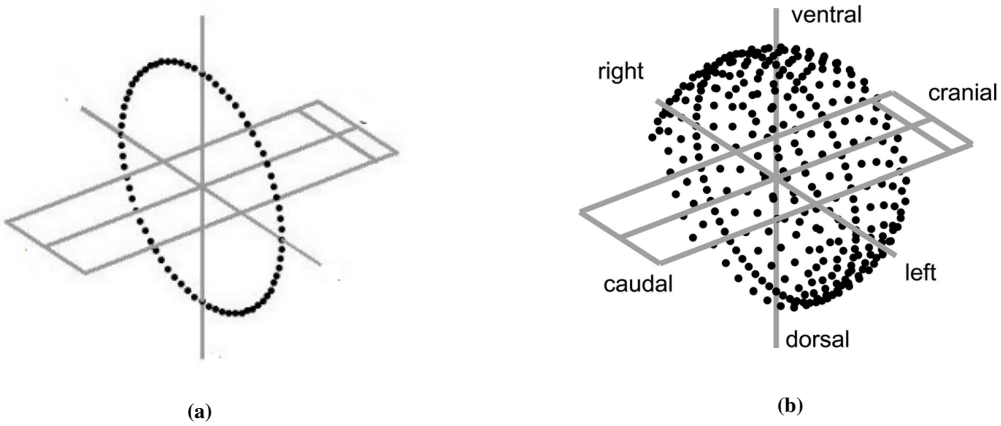


Figure 2.1: Candidate beam directions: a) coplanar and b) non-coplanar candidate beam directions. Focal spots relative to the treatment couch, schematically represented by dots. From [6]

Erasmus-iCycle starts with an empty plan and gradually adds beams. From the candidate beam search space, one beam is chosen by solving, for each of the not yet selected beams in the search space, an IMRT optimization problem, consisting of the candidate plus all the previously selected directions, as shown in figure 2.2. OAR dose is constrained to the results from the previous multi-criteria optimization and dose to the PTV is maximized. The orientation that is added improves (at least) one or more objectives, in order of priority, and is added to the IMRT problem definition, and so on, as in figure 2.2.

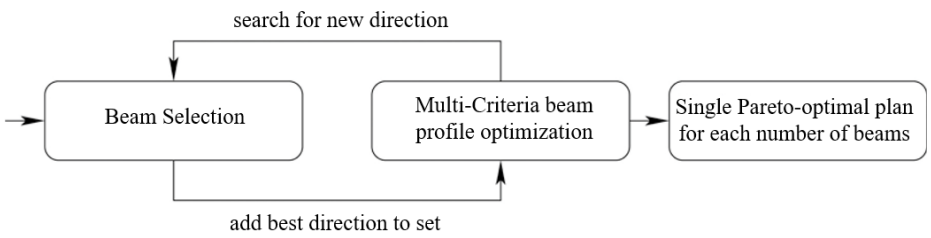


Figure 2.2: iCycle iterative beam angle selection and profile optimization. Each cycle starts with the selection of an optimal candidate beam; multi-criteria optimization of profiles is performed for to the previously selected beams plus the candidate and a Pareto-optimal IMRT plan is generated. The output from the latter optimization is used to define the problem for the next iteration, and so on. From [6].

Afterwards, the selected beam is added to the plan and a multi-criteria optimization is done to obtain a Pareto-optimal solution. Plans are generated with an increasing number of beams, until the maximum number of beams, set by the user, is reached.

Beam selection is a sequential process, meaning that for each added beam there is a plan where, at least, one goal is improved. The user can choose a posteriori which of the plans provides the best trade-off between treatment time, number of used beams, and plan quality [6].

2.1.3 From Erasmus-iCycle plan to Monaco deliverable plans

Currently, Erasmus-iCycle is clinically used as a pre-optimizer: optimized Erasmus-iCycle plans need to be reconstructed with a clinical TPS, in order to be deliverable plans with a linac [27, 30]. At the EMC, Erasmus-iCycle is coupled with Monaco TPS (version 5.11), introduced in section 1.5.1.

Erasmus-iCycle offers Pareto-optimal and clinically favorable plans, avoiding manual planning. At the EMC, a patient-specific Monaco TPS plan template is automatically generated using the dose distributions from the Erasmus-iCycle plan, in order to define all the settings needed for planning in the optimal manner for every patient [6]. This process of generating a Monaco template based on the Erasmus-iCycle plan is in-house called ”translation” and once it is developed, it can be automatically applied for all the patients.

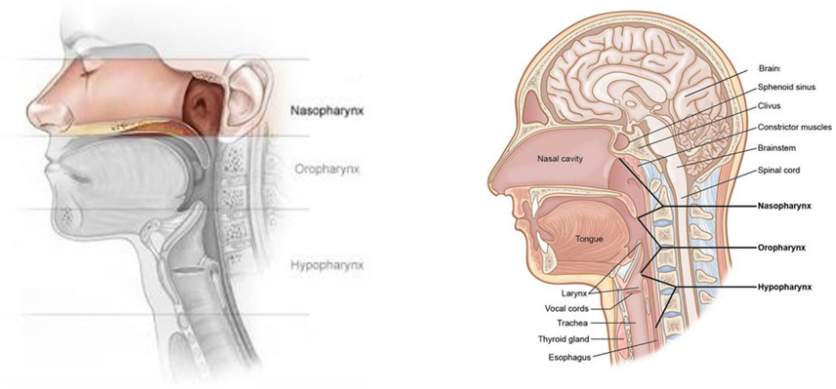
This process results in a fully automated, multi-criteria generation of IMRT and VMAT plans for clinical delivery at a linac. It allows to automatically generate plans with equal or higher plan quality as plans created by expert planners, while annulling or reducing planning time [27].

2.2 Introduction to investigated treatment sites

2.2.1 Nasopharyngeal carcinoma

Nasopharyngeal carcinoma (NPC) is a malignant tumor in the head-and-neck region originating from the epithelium of the nasopharynx. The nasopharynx is the superior part of the throat, from the upper surface of the oral cavity (soft palate) to the base of the skull. Posteriorly, the boundary are the muscles of the posterior pharyngeal wall and, above the oral cavity, extending to the posterior openings of the nasal cavities (choanae), represented in figure 2.3.

NPC typically metastases to cervical lymph nodes, which may be NPC initial presentation and what leads to diagnostic [31]. NPC spreads quickly to the paranasopharyngeal spaces, musculature and nodes. It may progress to the contralateral side, creating a bilateral tumor [32].



(a) (b)

Figure 2.3: Illustrations (median view) of the nasopharynx. From [7] and [8], respectively.

The incidence of NPC differs with geographic location and ethnic background. NPC is endemic to Southeast Asia and considered a rare tumor in Europe [33]. In low-risk populations, there is a bimodal peak distribution, in late adolescence/early adulthood (15–24 years) and adulthood (65–79 years) [34].

The nasopharynx is a deep area in the skull, very close to many organs. Structures near the nasopharynx include the nervous system organs such as the spinal cord, brainstem, brain, optic nerves, lenses, chiasm and retina; parallel organs such as the parotid glands and submandibular glands (SMGs), larynx, cochlea, esophagus, swallowing muscles (SwM), oral cavity; and the mandibula (serial organ) [31]. The division between parallel and serial organs is related to the effect of dose delivered to normal tissues. In parallel organs, function is preserved even if a certain fraction of the tissue is fully destroyed, so mean doses are of relevance. In serial organs, high doses are harmful even if they affect a small volume, so maximum doses are of relevance [35].

Treatment for NPC is difficult because of the intracranial nature of the tumors. Current RT treatments for NPC are coplanar VMAT, a combination of coplanar and non-coplanar VMAT arcs, or a differently selected beam arrangement chose by the planner, according to their clinical experience and the patient anatomy. As explained in section 1.3, this approach relies on planner knowledge and may lead to heterogeneous plan quality.

According to Wild et al. [4], patient-optimized non-coplanar plans improve OAR sparing but fully non-coplanar IMRT plans are time-consuming. Akbas et al. [36] found that hybrid IMRT and VMAT techniques improve VMAT plan quality, with limited increased delivery time. In this work we use automated plan generation to investigate the benefit of combining VMAT with patient-optimized IMRT beams.

2.2.2 Mediastinal lymphoma

Lymphomas are a group of haematopoietic malignant diseases, characterized by the uncontrolled proliferation of lymphocytes and lymph nodes cells (see figure 2.4), leading to the appearance of malignant cells capable of invading the body's tissues. Lymphomas can be divided in non-Hodgkin lymphoma (NHL) or Hodgkin lymphoma (HL), distinguishable by the presence of Reed-Sternberg cells in the first [37].

NHL may arise in lymph nodes anywhere in the body. HL typically begins in the upper part of the body: neck, axillae and chest (mediastinal area). Important structures in this area include the heart, lungs and both breasts. Both types of lymphoma can develop bilateral tumor masses [37, 38].

Lymphomas account for 3.5% of cancers diagnosed in Europe and are the most common cancer diagnosed in adolescents (21% of all cancers) [37].

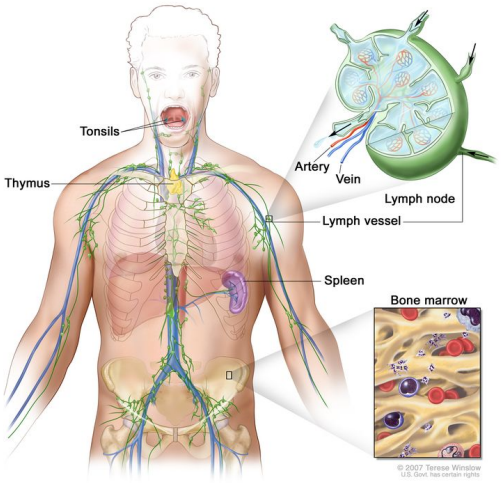


Figure 2.4: Illustration of the anatomy of the lymph system, including lymphatic vessels, organs and nodes. From [9].

Treatment depends on the type, stage, extension (smaller or larger) and location of the tumor, but standard treatment includes short-course chemotherapy and consolidation RT in pre-defined areas.

Radiotherapy for mediastinal lymphomas (ML) has evolved in recent years, allowing in decreasing radiation doses (from 40 to 30 Gy) and reducing target volumes. This decrease in dose and total irradiated volume leads to decreases in potential radiation-induced second cancers and other radiation-related effects.

In the heart, effects from late toxicity may result in non-ischemic cardiomyopathies, such as heart failure or left ventricular dysfunction [37]. Heart disease risk linearly increases with mean dose delivered to the heart [39]. There is also an enhanced risk of lung or breast cancer after mediastinal lymphoma RT [37]. The younger the patient was at the moment of treatment, the higher the risk; the elevated risk can be a concern up to 30 years after treatment [37]. De Bruin et al. [40], showed that reduction of total irradiated volume decreases chance of breast cancer.

For all the above-mentioned reasons, there is a high interest in controlling and reducing the dose to heart, breasts and lungs for these patients. Non-coplanar BAO IMRT and VMAT approaches have shown reduced dose in these organs over coplanar BAO IMRT and VMAT [11].

FaB-VMAT for treatment of mediastinal lymphoma

Full-arc butterfly VMAT (FaB-VMAT) was proposed by Levis et al. [10] for clinical lymphoma treatments. FaB-VMAT consists of one coplanar full arc with a non-coplanar perpendicular 60 ^{o} partial arc, as shown in figure 2.5.

This arc arrangement allows to deliver a fast treatment, with the use of non-coplanarity freedom. It allows lower mean dose to whole heart, with significantly lower estimated relative risk for coronary artery disease and chronic heart failure, and lower high doses for lungs, with comparable results for breasts mean and low dose and lungs mean and low dose, compared to conventional VMAT.

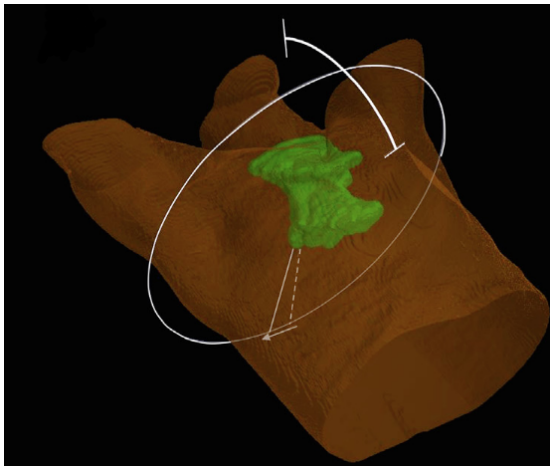
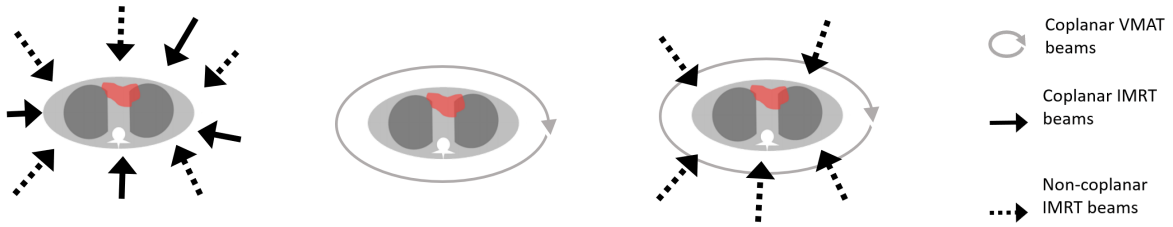


Figure 2.5: Representation of the full arc butterfly VMAT (FaB-VMAT). Adapted from [10].

2.3 VMAT+

VMAT+, i.e. coplanar VMAT supplemented with ≤ 5 non-coplanar IMRT beams, aims at combining short delivery times with some non-coplanarity provided by the IMRT beams. The VMAT+ technique was proposed for liver metastases by Sharfo et al. [41] and further investigated for prostate in [42].

In VMAT+ as applied in this thesis, the patient-specific non-coplanar IMRT beams are computer-optimized, as shown in figure 2.6. As presented by Sharfo et al., the maximum number of IMRT beams was limited to 5, to limit the treatment time. For VMAT+ generation, Erasmus-iCycle generated a coplanar VMAT and, sequentially, BAO was used to select the optimal non-coplanar beam to be added according to a similar procedure as explained in section 2.1.2, i.e. in the VMAT+2 one of the non-coplanar beams is the same beam as in the VMAT+1, and the second is the optimal non-coplanar beam selected to complement VMAT+1. After the selection of each beam, all beam profiles (VMAT and IMRT) are re-optimized, as described in section 2.1.2.



(a) IMRT **(b)** VMAT **(c)** VMAT+

Figure 2.6: Representation of a) IMRT, b) VMAT and c) VMAT+ techniques. Each arrow represent a possible beam: full arrows represent coplanar beams and dashed arrows represent non-coplanar beams. Adapted from [11].

2.4 Aim of the study

VMAT is a fast treatment, capable of delivering high coverage and conformality even for irregular targets [43, 44]. IMRT can also produce high-quality plans but it is a more time-consuming treatment. On the other hand, IMRT can benefit from optimized patient-specific beam arrangements [45], which can potentially further increase plan quality. Combining the two techniques in VMAT+ may result in higher quality plans, at the cost of only small increases in planning and delivery times, with improved OAR parameters [18]. In this thesis, we have investigated the impact of VMAT+ for the challenging nasopharyngeal carcinoma and mediastinal lymphoma treatments.

For each site, we analyzed the impact of the addition of several IMRT beams to VMAT compared to VMAT for nasopharyngeal carcinoma treatment, and compared to VMAT and FaB-VMAT, for mediastinal lymphoma.

The following two chapters of this thesis are separated for each investigated treatment site. Chapter 3 reports a description of patients, clinical protocol, generated plans, performed analyses and results for nasopharyngeal carcinoma study. Chapter 4 shows the same structure and data for mediastinal lymphoma. In chapter 5, overall conclusions about VMAT+ for these sites are presented.

3 Nasopharyngeal carcinoma

3.1 Material and Methods

3.1.1 Patients

This study is based on contoured CT scans of 11 nasopharyngeal carcinoma patients previously treated at the EMC. All patients were planned using a simultaneous integrated boost scheme, prescribing 70 Gy to the primary tumor and pathological lymph nodes, and 54.25 Gy to the elective nodal areas in 35 fractions. To this purpose, two PTVs were defined, as presented in figure 3.1. The first, PTV54.25, was created by uniform expansions of the primary CTVs and the elective lymph node CTVs by 0.5 cm (clipped at the patient surface by 0.5 cm). The boost PTV, PTV70, consisted of the primary CTVs, each expanded with a 0.5 cm margin (clipped at the patient surface by 0.5 cm). Average PTV70 volume was 323 ± 170 cc (range: 86-585 cc) and for PTV54.25 was 792 ± 306 cc (range: 184-1281 cc).

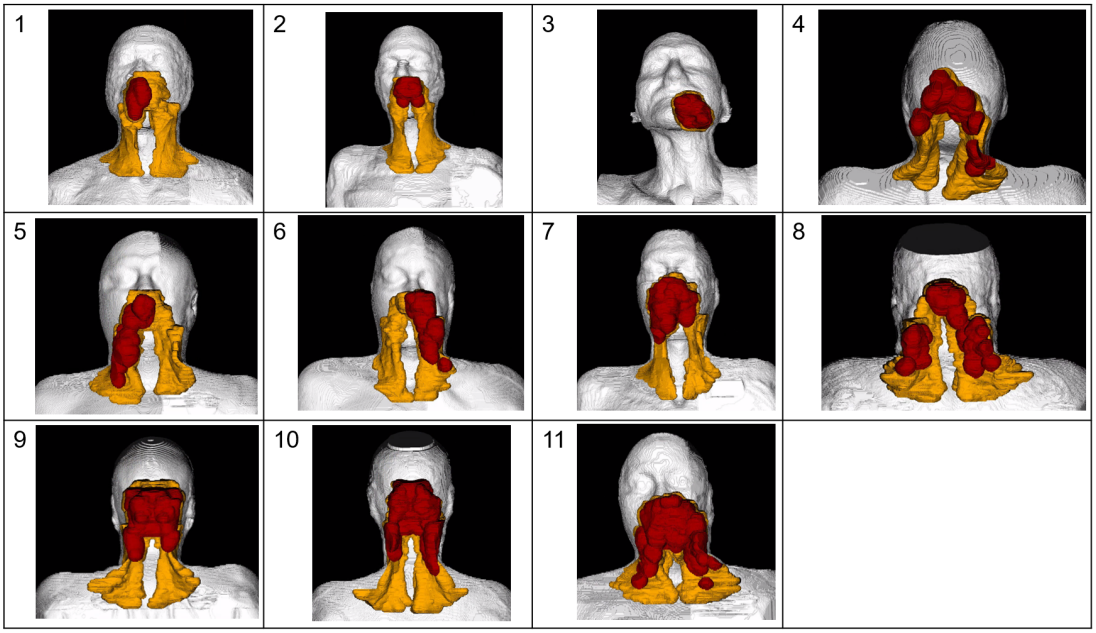


Figure 3.1: Study patients ordered from smallest to largest boost PTV volume. Red indicates the primary tumor and lymph nodes (PTV70), yellow indicates the elective nodal areas (PTV54.25).

Out of the 11 patients in this study, 10 were treated with dual-arc coplanar VMAT (patients 1-6 and 8-11; full arc) and 1 with dual-arc non-coplanar VMAT (patient 7; full arc, couch 0 ^{o}; partial arc, couch 90 ^{o}).

3.1.2 Clinical protocol

The EMC clinical planning protocol for NPC was followed in this study. Hard constraints (reported in brackets) were set for maximum irradiation for serial OARs (see section 2.2.1): optical nerves (< 55 Gy), chiasm (< 55 Gy), spinal cord (< 50 Gy), brainstem (< 60 Gy and volume receiving between 54-59 Gy less than 10 cc), brain (< 70 Gy, and the volume irradiated with more than 66.5 Gy as small as possible), retina (< 45 Gy) and mandible (< 72 Gy). PTV dose coverage, i.e. defined as the percentage of the PTV volume receiving at least 95% of the prescribed dose ($V_{95\%}$, should be over 98% and PTV hot spots, the volume receiving over 107% of the prescribed high dose ($V_{107\%}$), should be below 2 cc; CTV $V_{95\%}$ should be 100%.

For parallel OARs there were no hard constraints, but there was a preferred value based on knowledge of radiation induced side-effects. By order of priority, OARs and their respective preferred value (see section 2.2.1): both parotid glands ($D_{mean} < 26$ Gy), both submandibular glands ($D_{mean} < 39$ Gy), larynx ($D_{mean} < 45$ Gy), both cochleas ($D_{mean} < 45$ Gy), esophagus ($D_{mean} < 60$ Gy), swallowing muscles ($D_{mean} < 55$ Gy), mandible ($D_{0.03\ cc} < 72$ Gy), oral cavity ($D_{mean} < 50$ Gy) and lenses ($D_{0.03\ cc} < 5$ Gy).

3.1.3 Automated plan generation

All plans were generated with Erasmus-iCycle, using the same wish-list. The wish-list was developed based on the clinical protocol, using five training patients: initially tuned for 2 patients (not included in the study cohort) and afterwards further tuned on 3 study cohort patients, until the generated plans had a similar or superior quality than the clinical plans. Afterwards, the same wish-list was applied to four testing patients, from the patient cohort, to confirm that the wish-list was creating adequate plan quality. The final wish-list was used to generate automated treatment plans for all study patients.

Table 3.1 presents the resulting wish-list, with constraints and objectives in the upper and lower panels, respectively. For constraints, the first four lines restrict over- and mean dosage for PTV and minimum dose in the CTVs (right and left). The fifth line restricts dose in the patient to 107% of the prescribed dose. The following lines constraint dose fall-off between the PTV 70 and 54.25 Gy (PTV_2 Max) and in the volume 0-2.5 cm outside the combined PTV's volume. Smoothing constraints are added to avoid too steep dose gradients between subsequent voxels. For the brainstem, an equivalent uniform dose parameter (EUD) was also used to control the volume that receives higher dose (k=16, volume related parameter, the higher the k value is, the smaller the volume that will get high penalty); for the lenses, a constraint was added at 12 Gy.

Objective optimization starts with coverage of PTV low and high, with the logarithmic tumor control probability (LTCP) cost function [46]. Cochleas were given priority 3, although indicated at lower priority in the clinical protocol as they are very small organs and it was possible to optimize them the most without affecting the subsequent OARs. Priorities 4-9 mainly follow protocol order, with some alterations, to obtain a better balance of dose distribution and sparing. The mean dose was used as a cost function. Priority 10 uses an EUD to reduce the spinal cord and brainstem volumes that receive a high dose; priority 12 is used similarly, but for the mean dose in the brain (k=1). Priorities 11 and 13 reduce dose at 1.5 and 0.5 cm from the PTV, respectively in order to reach a more conformal dose distribution. Priority 14 optimizes higher dose volumes for the lenses and other neural structures. Finally, priorities 15-17 further minimize dose outside the PTV.

Table 3.1: Wish-list used in autoplanning for all NPC patients. [a]Maximum dose constraints were set lower than clinical requirements to account for voxel sampling during optimizations. [b] PTV expanded by 0.5 cm - combination of both PTVs; equivalent for the other rings. [c]For patients where PTV overlaps critical OARs, PTV_{opt} was constructed (see section 3.1.3). EUD indicates equivalent uniform dose, k indicates volume parameter. R indicates right and L indicates left. LTCP indicates the logarithmic tumor control probability, D_l=99% of prescribed dose and α indicates cell sensitivity. Goal and sufficient use is explained in [6].

Constraints

Structure	Type	Limit	Parameters
PTV70	maximum	74.9 Gy [a]	
PTV70	mean	70.7 Gy	
CTV R 54.25Gy	minimum	51.54 Gy	
CTV L 54.25Gy	minimum	51.54 Gy	
Patient	maximum	74.9 Gy	
PTV_2 Max	maximum	56.42 Gy	
Ring 2.5 cm from PTVs [b]	maximum	35 Gy	
Ring 0 cm from PTVs	maximum	70 Gy	
Spinal cord	maximum	48 Gy	
Brainstem	maximum	58 Gy	
Brainstem	EUD	54 Gy	k=16
Optical Nerve R	maximum	53 Gy	
Optical Nerve L	maximum	53 Gy	
Chiasm	maximum	53 Gy	
Brain	maximum	68 Gy	
Retina R	maximum	43 Gy	
Retina L	maximum	43 Gy	
Lens R	maximum	12 Gy	
Lens L	maximum	12 Gy	
Mandible	maximum	70 Gy	

Objectives

Priority	Structure	Type	Goal	Sufficient	Parameters
1	PTV54.25 [c]	LTCP	0.5	0.5	D_l=54.25 Gy, α=0.82
2	PTV70 [b]	LTCP	0.5	0.5	D_l=69.3Gy, α=0.82
3	Cochlea R	mean	35 Gy	35 Gy	
3	Cochlea L	mean	35 Gy	35 Gy	
4	Parotid R	mean	20 Gy		
4	Parotid L	mean	20 Gy		
5	Submandibular Gland R	mean	35 Gy		
5	Submandibular Gland L	mean	35 Gy		
6	Superior SwM	mean	25 Gy		
7	Middle SwM	mean	25 Gy		
7	Inferior SwM	mean	25 Gy		
8	Larynx	mean	35 Gy		
8	Oral Cavity	mean	35 Gy		
9	Esophagus	mean	40 Gy		
10	Spinal cord	EUD	25 Gy		k=12
10	Brainstem	EUD	25 Gy		k=12
11	Ring 1.5 cm from PTVs	EUD	10 Gy		k=8
12	Brain	EUD	25 Gy		k=1
13	Ring 0.5 cm from PTVs	EUD	10 Gy		k=8
14	Lens R	EUD	5 Gy		k=8
14	Lens L	EUD	5 Gy		k=8
14	Optical Nerve R	EUD	5 Gy		k=8
14	Optical Nerve L	EUD	5 Gy		k=8
14	Chiasm	EUD	5 Gy		k=8
14	Brain	EUD	5 Gy		k=8
14	Retina R	EUD	5 Gy		k=8
14	Retina L	EUD	5 Gy		k=8
15	Ring 4 cm from PTVs	EUD	5 Gy		k=8
16	Ring 5 cm from PTVs	EUD	5 Gy		k=8
17	External Ring	maximum	27.13 Gy		

3.1.3.1 Generated plans for plan comparisons and evaluations

Erasmus-iCycle was used to automatically generate all plans. First, to investigate the quality of the wish-list, an automatically generated and deliverable plan with the same beam configuration as clinically applied ($VMAT_t$ plans) was compared to the clinical plans (ClinVMAT plans). The $VMAT_t$ plans were based on Erasmus-iCycle dose distributions (VMAT plans) and translated in the Monaco TPS (version 5.11), as explained in section 2.1.3. The clinically applied beam configurations were used, meaning a dual-arc coplanar VMAT for patients 1 to 6 and 8 to 11 and a non-coplanar VMAT for patient 7.

After confirming that the wish-list was producing plans with similar quality as the ClinVMAT plans, Erasmus-iCycle was also used to automatically generate 6 plans per patient:

1. VMAT, 23 equiangular coplanar IMRT beams, used for all patients;
2. 5 VMAT+ plans, as VMAT+1, VMAT+2, VMAT+3, VMAT+4 and VMAT+5.

For VMAT+ plans, first a coplanar VMAT was simulated with 23 equi-angular IMRT beams; afterwards, the optimal non-coplanar beam was sequentially added generating plans with 1, 2, 3, 4 or 5 patient-specific non-coplanar IMRT beams, using BAO, as explained in section 2.3.

The applied beam energy was 6 MV. A pencil beam dose engine was used for Erasmus-iCycle plan generation and a Monte Carlo dose engine was used in the Monaco TPS translation.

3.1.4 Plan comparisons and evaluations

Automated plan generation in Erasmus-iCycle requires a treatment site specific wish-list. As for NPC there was no validated wish-list, it was necessary to create and compare it to clinical plans. Only after confirming that the wish-list was producing plans with a similar quality as the clinical plans it was possible to start generating VMAT+ plans.

Comparison of $VMAT_t$ plans and ClinVMAT

To ensure the high-quality of the automatically generated plans in Erasmus-iCycle, the $VMAT_t$ were compared to the ClinVMAT plans. The Monaco TPS translation (section 2.1.3) was configured in a way to maximize coverage and minimize hotspots for PTV70, and ensure that OARs received the same or even lower doses as the Erasmus-iCycle dose distributions.

To focus the plan comparison on dosimetric parameters, the plans were rescaled to the lower PTV70 coverage between $VMAT_t$ and ClinVMAT plans, for each patient.

Comparison of $VMAT_t$ and VMAT

The translation between Erasmus-iCycle plans to deliverable plans is a mainly automatic process, but still requires hands-on tunning. As the plans in this study were not meant to be delivered, there was no need to translate them.

To explore whether comparisons between VMAT and VMAT+ plans can be based on non-translated plans, i.e. Erasmus-iCycle dose distributions, it was necessary investigate if the $VMAT_t$ and VMAT plans were similar. If the differences between the plans are small, then this is feasible.

For this comparison the plans were rescaled to the lowest coverage out of the VMAT and $VMAT_t$ plans.

Comparison of VMAT and VMAT+

Plans for each patient were rescaled to the lowest PTV70 coverage of their VMAT and VMAT+ plans, i.e. the lowest coverage, per patient, of the VMAT, VMAT+1 to the VMAT+5. This method minimized bias related to PTV coverage when comparing OARs doses in different plans. For this comparison, patient 7 was excluded because the patient was clinically treated with a non-coplanar VMAT.

Plan evaluation in all above mentioned comparisons focused on dosimetric plan parameters and dose distributions. For the PTV70, the coverage ($V_{95\%}$ [%]), hot spots ($V_{107\%}$ [cc]) and conformity index (CI, defined as patient $V_{95\%}$ / $V_{\text{PTV cc}}$) were evaluated. A coverage above 98% is preferred ($V_{95\%} > 98\%$) but plans may be accepted with lower coverage in case of overlap with serial organs (e.g., brainstem, spinal cord, etc.) For the parallel organs, the mean dose (D_{mean}) was evaluated; for serial organs, the 0.03cc that receives the maximum volume is evaluated ($D_{0.03\,\text{cc}}$) as a more robust replacement of the D_{max} [47]. Overall patient dose volumes were evaluated for 10, 30 and 50 Gy ($V_{10\,\text{Gy}}$, $V_{30\,\text{Gy}}$ and $V_{50\,\text{Gy}}$, respectively).

Statistical analyses were performed with two-sided Wilcoxon signed-rank tests. Differences with p-value < 0.05 were considered statistically significant.

3.1.5 Subjective treatment plan selection

To further evaluate the different beam configurations, 4 reviewers were asked to independently compare and select, for each of the 10 patients, the best and second best plans, out of all 6 options (i.e. VMAT and VMAT+1 to VMAT+5). Reviewers had access to the plan parameters in the clinical plans for all parallel and serial OARs, brainstem and spinal cord $D_{0.03\text{cc}}$, brain D_{mean} and patient $V_{10\,\text{Gy}}$, $V_{30\,\text{Gy}}$ and $V_{50\,\text{Gy}}$.

Plan selection was performed twice: 1) considering only the plan quality and 2) considering the plan quality and delivery time. For the latter, treatment delivery times for the different beam geometries were estimated as provided in table 3.2. Estimations were based on previous research by Sharfo et al. [41]. For each beam configuration the presented time encompasses the time for radiation delivery, and for the VMAT+ the time to move the gantry from a certain angle to another, and the time to move the couch, which requires the technician to enter the treatment room.

The plan selection was analyzed by how many times a plan was chosen, as first and second option separately (in both performed plan selections, i.e. considering or not delivery time) and what plans were chosen the most. With the latter, a plan was considered ”the best” when at least 3 reviewers chose it as either first or second option. This last approach was used in order to investigate if there was consensus between the reviewers.

Table 3.2: Table with estimated VMAT and VMAT+ treatment times.

Plan	**VMAT**	**VMAT+1**	**VMAT+2**	**VMAT+3**	**VMAT+4**	**VMAT+5**
Time (min)	3	4.5	6	7.5	9	10.5

3.1.6 Weight of non-coplanar beams in VMAT+5 plans

Each beam in a treatment plan adds to the total PTV D_{mean}. For each of the VMAT+5 generated plans the contribution to PTV D_{mean} of the coplanar VMAT and each of the added beams was analyzed.

3.2 Results

3.2.1 Comparison of $VMAT_t$ and ClinVMAT

Prior to rescaling, PTV coverages and hotspot volumes for the $VMAT_t$ plans generated for the 11 patients ranged from 77.8 to 99.9% and 0 to 0.03 cc, respectively. For the clinically applied plans, PTV coverages and hotspot volumes ranged from 77.4 and 99.9% and 0 to 0.9 cc, respectively.

All results presented in the remainder of this section are based on rescaled plans, as described in section 3.1.4. Population PTV, OAR dose values and differences between ClinVMAT and $VMAT_t$ plans are reported in table 3.3. Differences per patient between ClinVMAT and $VMAT_t$ are represented in figure A.1a to A.1f.

$VMAT_t$ plans resulted in, on average, lower dose for all OARs. Average differences were statistically significant for left parotid D_{mean} (reduction by 3.2 ± 4.8 Gy, $p = 0.042$), left submandibular gland D_{mean} (reduction by 3.6 ± 4.0 Gy, $p = 0.004$), superior, middle and inferior swallowing muscles D_{mean} (reduction by 1.4 ± 1.9 Gy, $p = 0.042$, reduction by 3.3 ± 3.4 Gy, $p = 0.005$, reduction by 7.4 ± 7.4 Gy, $p < 0.001$), all in favor of $VMAT_t$ plans.

The comparisons between $VMAT_t$ and ClinVMAT demonstrate that automatically generated plans based on the developed wish-list (section 3.1.3) can be used for clinically relevant comparisons of VMAT+ with VMAT.

3.2.2 Comparison of VMAT and $VMAT_t$

Erasmus-iCycle prediction plans full-filled clinical requirements for the OARs. PTV coverage was above 98% ($V_{95\%} > 98\%$), and overdose spots ($V_{107\%}$) below 2 cc, for most patients (patients 1 to 6 and 8). PTV coverage was below 98% and hotspots were above 2 cc, for patient 7, 9, 10 and 11. For the first 3 patients, the PTV overlapped with the brain, the brainstem and the cord, limiting the coverage; for patient 11, the PTV70 surrounded the brainstem.

Average dosimetric values and differences between VMAT and $VMAT_t$ plans are reported in table 3.4 and show a large similarity. $VMAT_t$ plans resulted in higher coverage and no overdose spots. For most OARs the plans resulted in limited and mostly non-statistically significant differences.

Because of the high similarity between VMAT and $VMAT_t$, all comparisons between VMAT and VMAT+ described below were performed with not-translated plans to save time and workload related with translations.

Table 3.3: Comparison of dosimetric plan parameters for ClinVMAT and $VMAT_t$. Mean values, standard deviations (StD) and ranges refer to the 11 patients in the study. Statistically non-significant (NS) for p-value > 0.05. ClinVMAT indicates clinically applied VMAT. $VMAT_t$=automatically generated VMAT. For the brain it was not to possible to calculate statistical significance as the sample size was too small [12].

	ClinVMAT		**$VMAT_t$**		**ClinVMAT - $VMAT_t$**		
	Mean ± StD	**[Min, Max]**	**Mean ± StD**	**[Min, Max]**	**Mean ± StD**	**[Min, Max]**	**p - value**
PTV70							
$V_{95\%}$ [%]	95.2 ± 7.4	[77.7, 99.9]	95.2 ± 7.4	[77.7, 99.9]	0 ± 0	[-0.1, 0.1]	NS
$V_{107\%}$ [cc]	0.2 ± 0.3	[0, 1]	0 ± 0	[0, 0.1]	**0.2 ± 0.3**	[0, 0.9]	0.006
CI	1 ± 0.4	[0, 1.3]	1 ± 0.4	[0, 1.3]	0 ± 0.2	[-0.1, 0.4]	NS
$Parotid_R$							
D_{mean} [Gy]	36.2 ± 17.8	[9.2, 63.3]	35.3 ± 18.2	[7.8, 64.8]	0.9 ± 3.2	[-3.7, 8.3]	NS
$Parotid_L$							
D_{mean} [Gy]	43.6 ± 14.8	[24.5, 67.3]	40.5 ± 13.8	[24.6, 66.3]	**3.2 ± 4.8**	[-2.5, 13.7]	0.042
SMG_R							
D_{mean} [Gy]	56.7 ± 14.3	[34.6, 70.1]	54.1 ± 14.9	[34.6, 70.6]	2.5 ± 4.2	[-1.7, 11]	NS
SMG_L							
D_{mean} [Gy]	55.2 ± 13.6	[37, 69.7]	51.5 ± 14.7	[34.1, 70]	**3.6 ± 4**	[-0.3, 10.2]	0.004
Larynx							
D_{mean} [Gy]	38.4 ± 12.2	[11.6, 55.5]	31 ± 9.4	[11.3, 43.1]	**7.3 ± 10.3**	[-7.3, 31.4]	0.024
$Cochlea_R$							
D_{mean} [Gy]	37.4 ± 17.3	[12.1, 68.8]	37 ± 11	[17.6, 55.1]	0.3 ± 8.4	[-8.2, 18.2]	NS
$Cochlea_L$							
D_{mean} [Gy]	42.4 ± 15.2	[23.8, 67.8]	38.7 ± 6.8	[32.8, 54.1]	3.8 ± 11.4	[-8.9, 26.3]	NS
Esophagus							
D_{mean} [Gy]	25.1 ± 12.9	[0.3, 41.3]	23.5 ± 11.2	[0.2, 37.9]	1.7 ± 6.5	[-12.8, 11.4]	NS
Superior SwM							
D_{mean} [Gy]	65.9 ± 4.9	[56.2, 72.5]	64.6 ± 5.6	[55.6, 70]	**1.4 ± 1.9**	[-1.3, 5.3]	0.042
Middle SwM							
D_{mean} [Gy]	53.9 ± 12.7	[24.7, 70.5]	50.6 ± 13.1	[24.4, 70]	**3.3 ± 3.4**	[-0.5, 8.3]	0.005
Inferior SwM							
D_{mean} [Gy]	36.9 ± 18.1	[1.8, 58.8]	29.5 ± 15	[1.6, 55.2]	**7.4 ± 7.4**	[0.2, 23.7]	< 0.001
Mandible							
$D_{0.03\,cc}$ [Gy]	70.3 ± 5.3	[59.3, 74.7]	69.2 ± 6.3	[52.1, 72.9]	1.1 ± 2.6	[-2.6, 7.2]	NS
Oral Cavity							
D_{mean} [Gy]	40.3 ± 5.6	[33, 49.4]	39.2 ± 5.5	[31, 48.9]	1 ± 2.4	[-2.5, 4.7]	NS
$Lens_L$							
$D_{0.03\,cc}$ [Gy]	5.6 ± 3.5	[1, 12.6]	4.6 ± 2.4	[0.8, 7.7]	1 ± 2.4	[-2.3, 5.8]	NS
$Lens_R$							
$D_{0.03\,cc}$ [Gy]	5.5 ± 3.4	[1, 12.4]	5.3 ± 3	[0.8, 10.4]	0.2 ± 3.2	[-5.7, 5.3]	NS
Patient							
$V_{10\,Gy}$	4670.6 ± 2369	[7.5, 6818.9]	4407.5 ± 2256.7	[7.4, 7857.7]	263.1 ± 903.3	[-1038.7, 2287.1]	NS
$V_{30\,Gy}$	2063 ± 1017.9	[7, 2844]	1941.7 ± 1055.8	[7, 3576.4]	121.2 ± 354.3	[-732.5, 632]	NS
$V_{50\,Gy}$	923.7 ± 448.4	[8.9, 1252.8]	934.7 ± 522.3	[8.9, 1703.7]	-11 ± 193.9	[-450.9, 136.2]	NS
Spinal Cord							
$D_{0.03\,cc}$ [Gy]	40 ± 7.3	[25.2, 48.4]	39 ± 6.2	[28, 46.1]	1 ± 6.9	[-13.9, 12.3]	NS
Brainstem							
$D_{0.03\,cc}$ [Gy]	49.9 ± 9.7	[26.2, 58.2]	51.7 ± 8.1	[37.6, 60]	-1.9 ± 4	[-11.4, 3.2]	NS
Brain							
D_{mean} [Gy]	9.3 ± 3.7	[5.6, 14.1]	8.1 ± 3.1	[4.9, 12.1]	1.2 ± 0.7	[0.6, 2.3]	NS
$Optical\ Nerve_L$							
$D_{0.03\,cc}$ [Gy]	31.4 ± 19.7	[3, 52.2]	28 ± 22.4	[2.4, 56.1]	3.3 ± 9.2	[-11.5, 19.9]	NS
$Optical\ Nerve_R$							
$D_{0.03\,cc}$ [Gy]	29.6 ± 20.2	[2.1, 53]	25.9 ± 22.6	[1.7, 57.6]	3.7 ± 7.5	[-6.7, 20]	NS
Chiasm							
$D_{0.03\,cc}$ [Gy]	27.2 ± 20.6	[3, 54]	25.1 ± 23.1	[2.5, 54.7]	2.1 ± 6.2	[-3.5, 16.1]	NS
$Retina_L$							
$D_{0.03\,cc}$ [Gy]	18.8 ± 18.7	[1.7, 55.4]	12.4 ± 11.1	[1.4, 33.5]	6.4 ± 8.4	[-0.6, 21.9]	NS
$Retina_R$							
$D_{0.03\,cc}$ [Gy]	20.7 ± 19.5	[1.5, 56.8]	15 ± 12.6	[1.2, 38.5]	5.8 ± 8.2	[-0.9, 18.3]	NS

Table 3.4: Comparison of dosimetric plan parameters of VMAT (non-translated iCycle VMAT plans) and $VMAT_t$ plans (clinically deliverable plans: iCycle followed by translation in Monaco). Mean values, standard deviations (StD) and ranges refer to the 11 patients in the study. Statistically non-significant (NS) for p-value > 0.05. For the brain it was not to possible to calculate statistical significance as the sample size was too small [12].

	VMAT		**$VMAT_t$**		**VMAT - $VMAT_t$**		
	Mean ± StD	**[Min, Max]**	**Mean ± StD**	**[Min, Max]**	**Mean ± StD**	**[Min, Max]**	**p - value**
PTV70							
$V_{95\%}$ [%]	93 ± 11.6	[64.6, 99.8]	95.3 ± 7.3	[77.8, 100]	-2.3 ± 4.4	[-13.2, 1]	NS
$V_{107\%}$ [cc]	1.7 ± 2.3	[0, 7]	0 ± 0	[0, 0]	**1.7 ± 2.3**	[0, 7]	< 0.001
CI	1.1 ± 0.2	[0.7, 1.2]	1.1 ± 0.1	[0.8, 1.3]	-0.1 ± 0.1	[-0.2, 0.1]	0.014
$Parotid_R$							
D_{mean} [Gy]	34.5 ± 15	[12.8, 57.7]	35.3 ± 18.2	[7.8, 64.8]	-0.8 ± 4	[-9.3, 5]	NS
$Parotid_L$							
D_{mean} [Gy]	39.8 ± 12.2	[25, 59.2]	40.5 ± 13.8	[24.4, 66.3]	-0.7 ± 2.3	[-7.4, 0.6]	NS
SMG_R							
D_{mean} [Gy]	53.6 ± 13.8	[35.2, 68.8]	54.1 ± 14.8	[34.7, 69.9]	-0.5 ± 1.4	[-3.9, 0.9]	NS
SMG_L							
D_{mean} [Gy]	50.6 ± 14	[35.2, 70.2]	51.5 ± 14.8	[34.1, 70]	-0.9 ± 2.2	[-6.7, 1.1]	NS
Larynx							
D_{mean} [Gy]	33.3 ± 8.2	[12.2, 42.7]	31 ± 9.3	[11.5, 43]	2.2 ± 3.6	[-1.1, 9.9]	NS
$Cochlea_R$							
D_{mean} [Gy]	40.5 ± 13.7	[20.2, 59.7]	37 ± 11	[17.6, 55.1]	**3.5 ± 4.3**	[-1, 10.8]	0.019
$Cochlea_L$							
D_{mean} [Gy]	41.3 ± 10.8	[34.7, 61.1]	38.7 ± 6.8	[32.8, 54.2]	2.6 ± 5.3	[-2.6, 14.1]	NS
Esophagus							
D_{mean} [Gy]	26.9 ± 11.7	[0, 39.7]	23.5 ± 11.2	[0.2, 37.9]	**3.4** ± 4.5	[-0.6, 12.4]	0.019
Superior SwM							
D_{mean} [Gy]	63.3 ± 5	[53.8, 71.1]	64.6 ± 5.6	[55.9, 70.1]	-1.3 ± 1.9	[-4.7, 2]	NS
Middle SwM							
D_{mean} [Gy]	50.3 ± 11.6	[25.5, 71]	50.6 ± 13.1	[24.6, 70]	-0.3 ± 3.4	[-8.6, 5.7]	NS
Inferior SwM							
D_{mean} [Gy]	31.5 ± 14.3	[2.6, 56.2]	29.5 ± 15	[1.6, 55.3]	**2** ± 2.1	[-0.7, 7]	0.005
Mandible							
$D_{0.03\ cc}$ [Gy]	68.1 ± 5.8	[53.7, 71.4]	69.2 ± 6.2	[52.5, 72.9]	**-1.1 ± 1.3**	[-3.2, 1.2]	0.019
Oral Cavity							
D_{mean} [Gy]	41 ± 5	[32.3, 48.5]	39.3 ± 5.4	[31.3, 48.8]	**1.7 ± 1.5**	[-0.6, 3.6]	0.005
$Lens_R$							
$D_{0.03\ cc}$ [Gy]	7.1 ± 3.7	[0.6, 11.4]	5.3 ± 3	[0.8, 10.4]	**1.8 ± 1.6**	[-0.3, 4.2]	0.01
$Lens_L$							
$D_{0.03\ cc}$ [Gy]	6.5 ± 3.5	[0.8, 10.7]	4.6 ± 2.4	[0.8, 7.7]	**1.9 ± 1.5**	[0, 3.8]	0.004
Patient							
$V_{10\ Gy}$	4957.6 ± 1566.4	[1668.8, 7786.9]	5068.3 ± 1642.8	[1641.7, 7870.8]	**-110.8 ± 199**	[-673.9, 35.9]	0.042
$V_{30\ Gy}$	2448.8 ± 857.2	[572.2, 3851.9]	2273.9 ± 831.4	[532.5, 3590.5]	**175 ± 145.5**	[-105.3, 364.9]	0.007
$V_{50\ Gy}$	1194.2 ± 448.5	[262.2, 1881.4]	1100.1 ± 419.8	[248, 1716.7]	**94.1 ± 46.8**	[14.2, 164.8]	< 0.001
Spinal Cord							
$D_{0.03\ cc}$ [Gy]	42.6 ± 6	[29.6, 49.5]	38.9 ± 6	[28.1, 46.3]	**3.7 ± 3**	[0.3, 10.3]	< 0.001
Brainstem							
$D_{0.03\ cc}$ [Gy]	52.5 ± 7.7	[38.4, 59.5]	51.7 ± 8.2	[37.5, 60]	0.7 ± 2	[-2.3, 4.6]	NS
Brain							
D_{mean} [Gy]	8.8 ± 3.6	[5.1, 14]	8.1 ± 3.1	[4.9, 12.1]	0.7 ± 0.6	[0.2, 1.9]	NS
$Optical\ Nerve_R$							
$D_{0.03\ cc}$ [Gy]	27.8 ± 21.3	[2.4, 54.6]	25.9 ± 22.6	[1.7, 57.6]	1.9 ± 3.2	[-3, 7.8]	NS
$Optical\ Nerve_L$							
$D_{0.03\ cc}$ [Gy]	30.5 ± 21.5	[3.6, 54.4]	28 ± 22.4	[2.5, 56.1]	**2.5 ± 3.7**	[-2.2, 10.8]	0.039
Chiasm							
$D_{0.03\ cc}$ [Gy]	26.3 ± 22	[3.9, 54.5]	25.1 ± 23.1	[2.6, 54.9]	1.2 ± 2.6	[-3.3, 5.9]	NS
$Retina_R$							
$D_{0.03\ cc}$ [Gy]	16.6 ± 13.9	[1.6, 41.9]	15 ± 12.7	[1.2, 38.7]	1.6 ± 1.8	[-1.1, 3.2]	NS
$Retina_L$							
$D_{0.03\ cc}$ [Gy]	14.6 ± 12.6	[2.3, 39]	12.4 ± 11.1	[1.5, 33.7]	**2.2 ± 1.7**	[0.8, 5.3]	0.031

3.2.3 Comparison of VMAT and VMAT+

The automatically generated VMAT and VMAT+ plans were evaluated for clinical acceptability regarding target coverage and OAR constraints. In patients 9 and 10, PTV70 overlapped with either the brain, brainstem or cord, limiting PTV coverage and increasing overdose spots. For these two patients, PTV70 coverage was lower than 98% and the overdose volume exceeded the clinical constraint ($V_{107\%} > 2$cc), but coverage was comparable to clinical and smaller high dose areas could be obtained after translation, as described previously. For all 10 analyzed patients, OAR doses were within constraint.

For each of the patients, PTV doses after rescaling were highly comparable, with non-statistically significant differences for PTV hotspot volumes between the 6 compared plans (VMAT and 5 VMAT+ plans), as seen in figure C.1a and C.1b, respectively. Thus, the main focus of comparison will be OAR doses.

Figure 3.2 compares dose distributions for an example patient. Comparisons between VMAT and VMAT+ plans for each OAR and patient are presented in figure 3.3. Differences in average, standard deviation and range between VMAT and VMAT+ plans parameters are in appendix B, table B.1 and B.2. Mutual comparisons for all OARs and plans are reported in appendix C.

This section is now divided in 3 parts. First, 1) the average results based on all patients and OARs will be presented for the comparison between VMAT and VMAT+, followed by 2) an analysis for each separate OAR, for all beam configurations and patients, and finally, 3) an analysis for one selected patient. Discussion of results is focused on statistically significant differences and overall trends that possibly have clinical relevance.

3.2.3.1 Population analysis: VMAT+ vs VMAT

- Although not always statistically significant for the patient population and probably also not always clinically relevant, VMAT+ had generally lower population average values than VMAT, for parotids, SMG, esophagus, left cochlea and superior SwM mean doses, mandible $D_{0.03\,cc}$, oral cavity D_{mean}, patient $V_{30\,Gy}$ and spinal cord $D_{0.03\,cc}$ (see figure 3.3a, 3.3b, 3.3c, 3.3d, 3.3e, 3.3f, 3.3h, 3.3i, respectively, and figure C.1).

- VMAT had generally, limited and not statistically significant, lower population average values than VMAT+, for larynx, right cochlea, inferior swallowing muscles mean doses (see figure 3.3c, 3.3d, 3.3e, respectively, and figure C.1), and probably sometimes clinically relevant lower population average values for both lenses $D_{0.03\,cc}$ and brain D_{mean} (see figure 3.3g and 3.3j, respectively, and figure C.1). VMAT was only statistically significantly better than VMAT+ for patient $V_{10\,Gy}$ (see figure 3.3h, and figure C.1).

- VMAT+5 was overall superior to VMAT (see figure 3.3), with statistically significant improvements for right and left parotid D_{mean} (3.0 ± 1.7 Gy, $p = 0.002$, and 2.5 ± 1.5 Gy, $p = 0.002$), left submandibular gland D_{mean} (0.4 ± 0.3 Gy, $p = 0.02$), superior and middle swallowing muscle D_{mean} (0.4 ± 0.4 Gy, $p = 0.002$, and 0.5 ± 0.4 Gy, $p = 0.02$, respectively) and patient $V_{30\,Gy}$ and $V_{50\,Gy}$ (113.2 ± 73.5 Gy, $p = 0.004$, and 29.6 ± 21.8 Gy, $p = 0.01$, respectively).

- VMAT performed better than VMAT+5, with statistically significant difference, only for patient $V_{10\,Gy}$ (-268.4 ± 229.2, $p = 0.01$), as also seen for patient 3, in the sagittal view in figure 3.2.

- For the highest priority OARs, the parotids, each new added beam results in statistically significant improvements, compared to the plan with one less beam (i.e. VMAT+3 improves, with statistically significance, VMAT+2 parotids D_{mean}) from VMAT to VMAT+5 (see figure 3.3a, and figure C.1c and C.1d).

- VMAT+1 was, on average, the best plan for the esophagus and left lens, with statistically significant differences compared to VMAT (1.4 ± 2.5, $p = 0.04$, and 0.4 ± 0.5, $p = 0.004$, respectively, see table B.1).

- Patients with small and unilateral tumors (i.e. patient 1, 2 and 3, see figure 3.1) gained more from VMAT+ plans for SMGs and oral cavity than the other patients, and resulted in similar D_{mean} values as in VMAT, for esophagus and inferior SwM (figure 3.3b and 3.3f, and figure 3.3c and 3.3e, respectively).

- Added number of beams resulted in increasingly superior sparing for the parotids and patient $V_{30\,Gy}$ and $V_{50\,Gy}$, with statistically significant differences, see figure C.1c, C.1d, C.1s and C.1t, respectively. From VMAT+3 to VMAT+4 the right submandibular gland, the swallowing muscles, patient $V_{30\,Gy}$ and the brainstem, improved with statistical significance, see figure C.1e, C.1k, C.1l, C.1m, C.1s and C.1v, respectively.

- There were no statistically significant differences between VMAT+5 and VMAT+3 and VMAT+4 for the larynx, the esophagus, both cochleas, the inferior SwM, the mandible, both lenses and patient $V_{10\,Gy}$, see figure C.1. For VMAT+4, the middle and superior SwM, the oral cavity, patient $V_{50\,Gy}$, the spinal cord, the brainstem and the brain, also resulted in similar doses to VMAT+5 (no statistically significant difference).

- There were no statistically significant differences between VMAT+5 and VMAT+1 and VMAT+2 for the right SMG, the esophagus, the right cochlea, the inferior SwM, the mandible, both lenses, the spinal cord, the brain and the CI, see figure C.1. For VMAT+1 there was also no statistically significant difference for the brainstem.

- OAR sparing is patient-specific. Most patients benefit from VMAT+, but other than parotids, there is usually no clear trend.

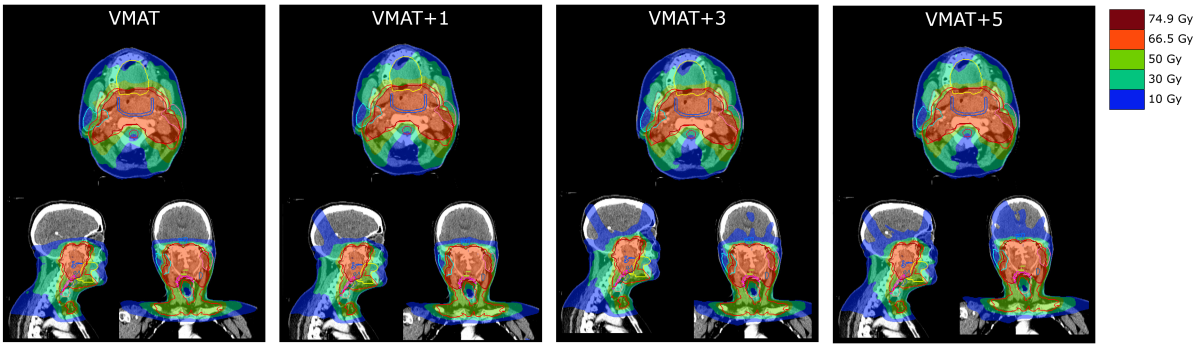


Figure 3.2: Dose distributions for patient 11. PTV70 delineated in red. Left parotid delineated in bright blue, right parotid in pink, right SMG in bright blue, left SMG in dark blue, superior SwM in blue, middle SwM in green, inferior SwM in pink, oral cavity in yellow, mandible in brown and spinal cord in dark red.

3.2.3.2 Per OAR analysis

- **Parotids**: Adding beams decreased the value for D_{mean} for both parotids (see figure 3.3a). VMAT+5 resulted in the lowest D_{mean}, with statistically significant difference to VMAT and all other VMAT+ plans (figure C.1c and C.1d, respectively).

- **Submandibular Glands**: Differences were limited and mostly non statistically significant, except for patient 1 that had a large (and increasing) improvement with each VMAT+ plan (see figure 3.3b).

- **Cochleas**: For most patients, for both cochleas, the difference between plans is either very small or the D_{mean} value is lower for one of the VMAT+ plans; for patient 6 right cochlea D_{mean} is better with VMAT (see figure 3.3d).

- **Swallowing Muscles**: On average, VMAT+4 and VMAT+5 performed the best for the superior and middle swallowing muscles, with statistically significant improvements compared to the other plans, but for most patients the differences were small (figure 3.3e). For the inferior swallowing muscles, VMAT performed better for patients with a lower VMAT D_{mean} (pats. 2, 3 and 4, smaller tumors, see figure 3.1) and VMAT+ plans performed better for patients receiving with a higher VMAT D_{mean} (pats. 8, 9 and 10, larger tumors).

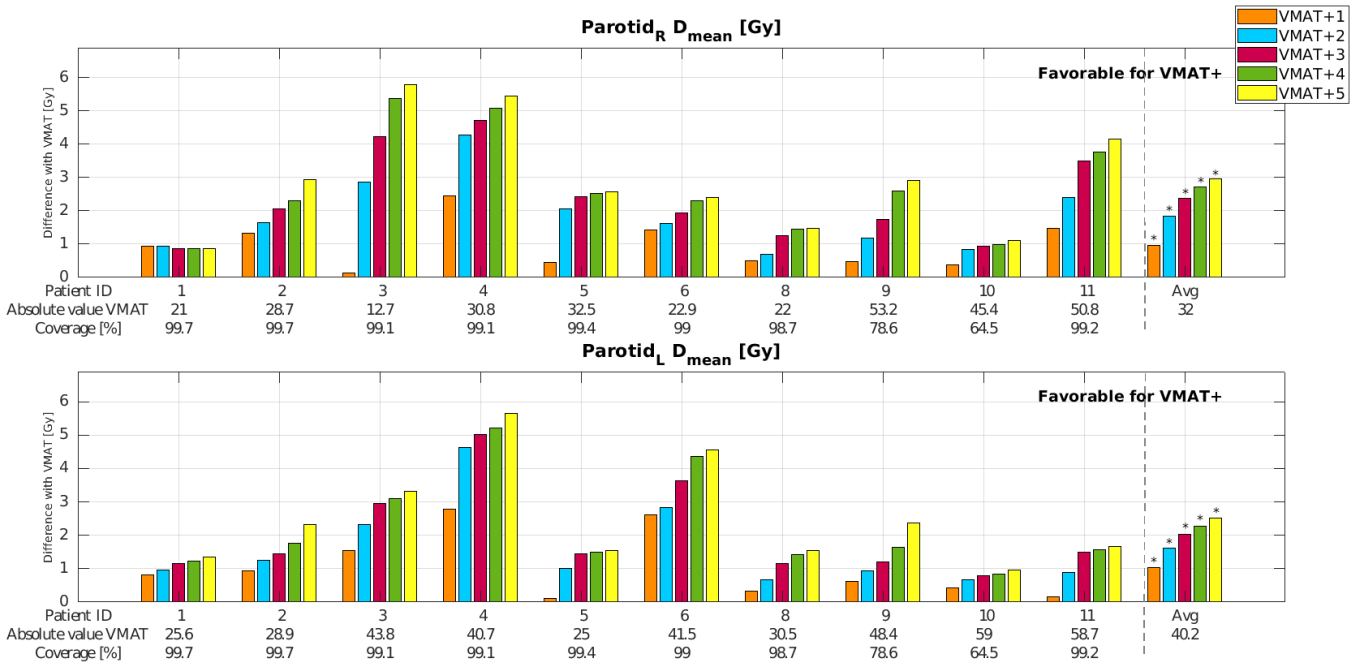
- **Lenses**: VMAT+1 was the best plan for the left lens, with statistically significant improvements compared to VMAT (figure 3.3g).

- **Patient Doses**: VMAT performed better for $V_{10\,Gy}$, with statistically significant differences to the VMAT+ plans, see figure 3.3h and figure C.1r. Adding beams on average improved higher patient doses ($V_{30\,Gy}$ and $V_{50\,Gy}$), generally with statistically significant improvements (figure C.1s and C.1t). For patients with larger, bilateral tumors, there is a clear improvement for $V_{30\,Gy}$ and $V_{50\,Gy}$ with each added beam.

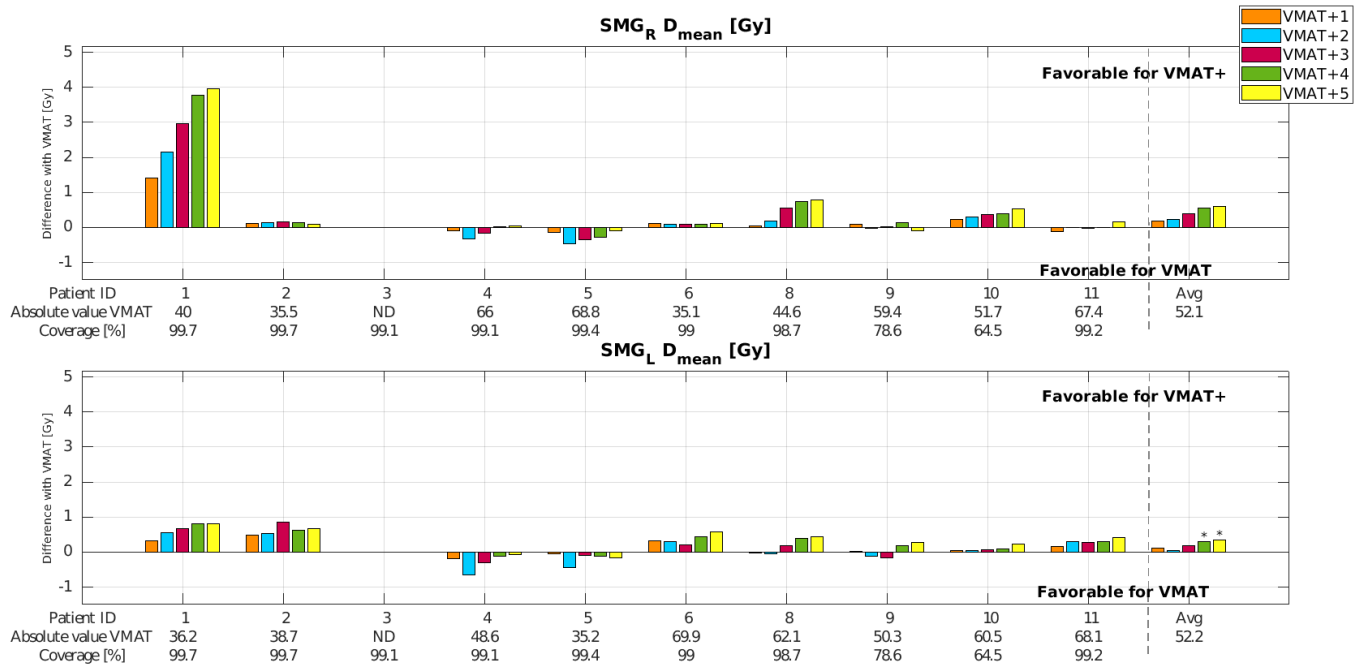
- **Brain**: VMAT was clearly the best for brain D_{mean}, see figure 3.3j.

For the larynx, esophagus, mandible, oral cavity, spinal cord, brainstem and the conformity index, average population differences between plans were negligible.

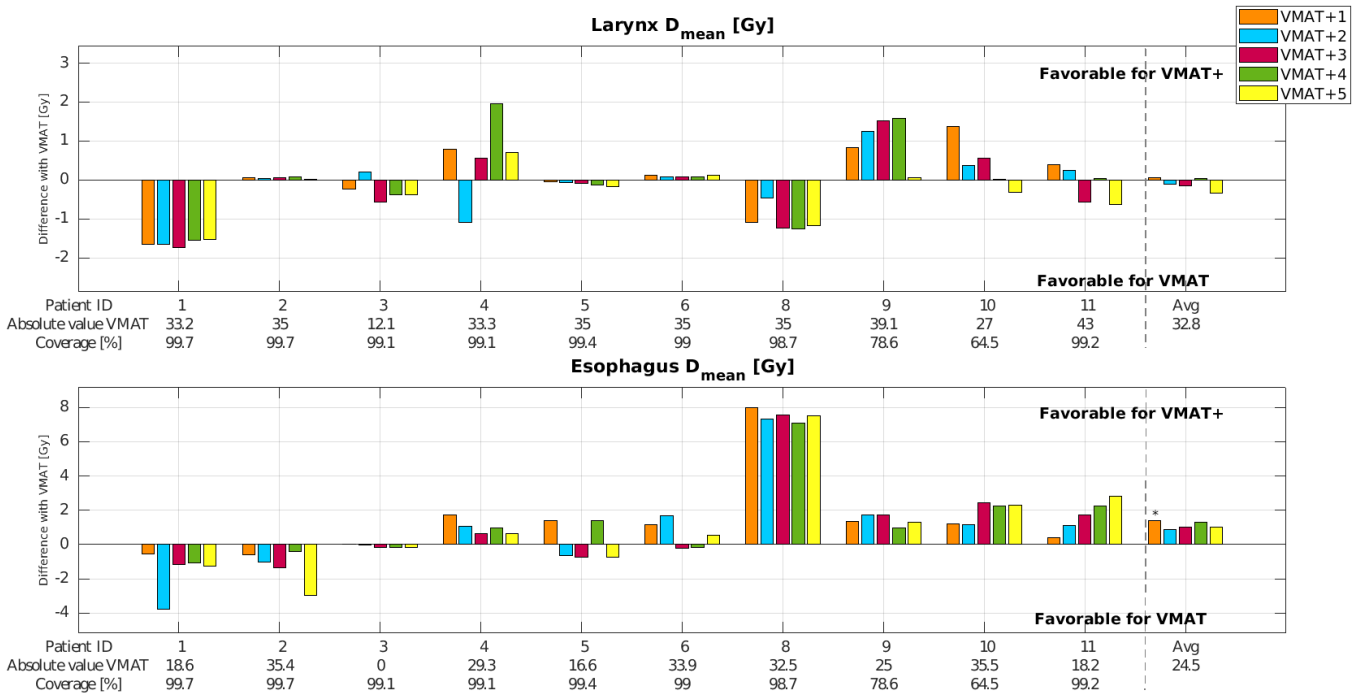
For some OARs, although there were, on average, no large differences between the 6 plans, some patients benefited from one or more VMAT+ plans. For example, for the esophagus, on average, all plans were similar, but patient 8 received 8 Gy less than VMAT with VMAT+1 (figure 3.3c). The same happened with the oral cavity where patient 1 and 3, both small, unilateral tumors, benefited from VMAT+ plans, with increased sparing with added beams, see figure 3.3f.


Parotid$_R$ D$_{mean}$ [Gy]
VMAT+1
VMAT+2
VMAT+3
VMAT+4
VMAT+5
Favorable for VMAT+
Difference with VMAT [Gy]
Patient ID 1 2 3 4 5 6 8 9 10 11 Avg
Absolute value VMAT 21 28.7 12.7 30.8 32.5 22.9 22 53.2 45.4 50.8 32
Coverage [%] 99.7 99.7 99.1 99.1 99.4 99 98.7 78.6 64.5 99.2
Parotid$_L$ D$_{mean}$ [Gy]
Favorable for VMAT+
Difference with VMAT [Gy]
Patient ID 1 2 3 4 5 6 8 9 10 11 Avg
Absolute value VMAT 25.6 28.9 43.8 40.7 25 41.5 30.5 48.4 59 58.7 40.2
Coverage [%] 99.7 99.7 99.1 99.1 99.4 99 98.7 78.6 64.5 99.2

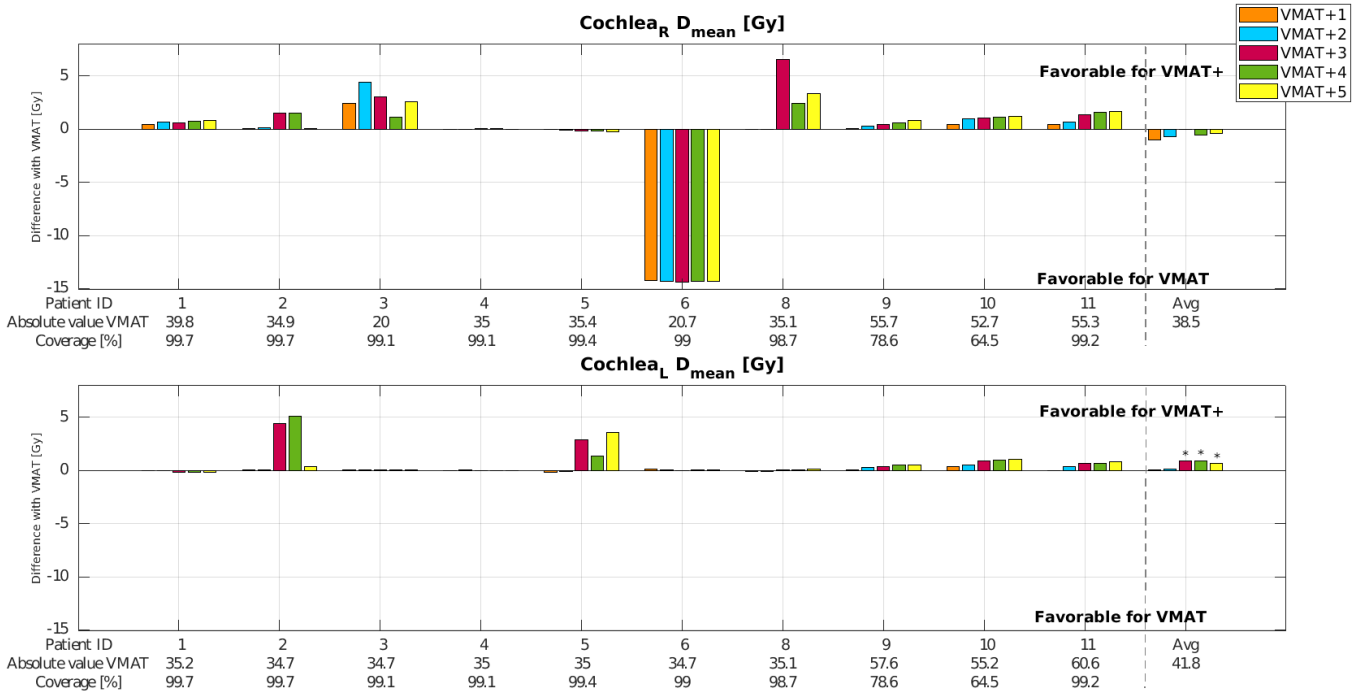
(a)


SMG$_R$ D$_{mean}$ [Gy]
VMAT+1
VMAT+2
VMAT+3
VMAT+4
VMAT+5
Favorable for VMAT+
Favorable for VMAT
Difference with VMAT [Gy]
Patient ID 1 2 3 4 5 6 8 9 10 11 Avg
Absolute value VMAT 40 35.5 ND 66 68.8 35.1 44.6 59.4 51.7 67.4 52.1
Coverage [%] 99.7 99.7 99.1 99.1 99.4 99 98.7 78.6 64.5 99.2
SMG$_L$ D$_{mean}$ [Gy]
Favorable for VMAT+
Favorable for VMAT
Difference with VMAT [Gy]
Patient ID 1 2 3 4 5 6 8 9 10 11 Avg
Absolute value VMAT 36.2 38.7 ND 48.6 35.2 69.9 62.1 50.3 60.5 68.1 52.2
Coverage [%] 99.7 99.7 99.1 99.1 99.4 99 98.7 78.6 64.5 99.2

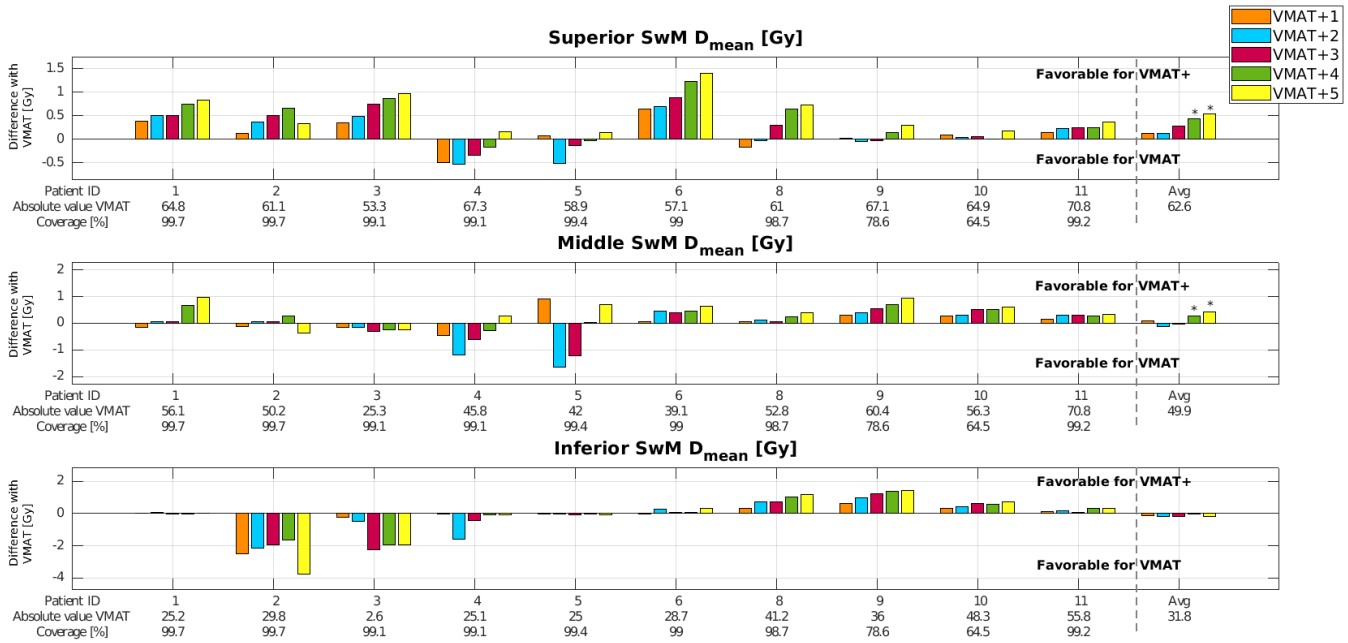
(b)


Larynx D mean [Gy]
VMAT+1
VMAT+2
VMAT+3
VMAT+4
VMAT+5
Favorable for VMAT+
Favorable for VMAT
Difference with VMAT [Gy]
Patient ID 1 2 3 4 5 6 8 9 10 11 Avg
Absolute value VMAT 33.2 35 12.1 33.3 35 35 35 39.1 27 43 32.8
Coverage [%] 99.7 99.7 99.1 99.1 99.4 99 98.7 78.6 64.5 99.2
Esophagus D mean [Gy]
Favorable for VMAT+
Favorable for VMAT
Difference with VMAT [Gy]
Patient ID 1 2 3 4 5 6 8 9 10 11 Avg
Absolute value VMAT 18.6 35.4 0 29.3 16.6 33.9 32.5 25 35.5 18.2 24.5
Coverage [%] 99.7 99.7 99.1 99.1 99.4 99 98.7 78.6 64.5 99.2

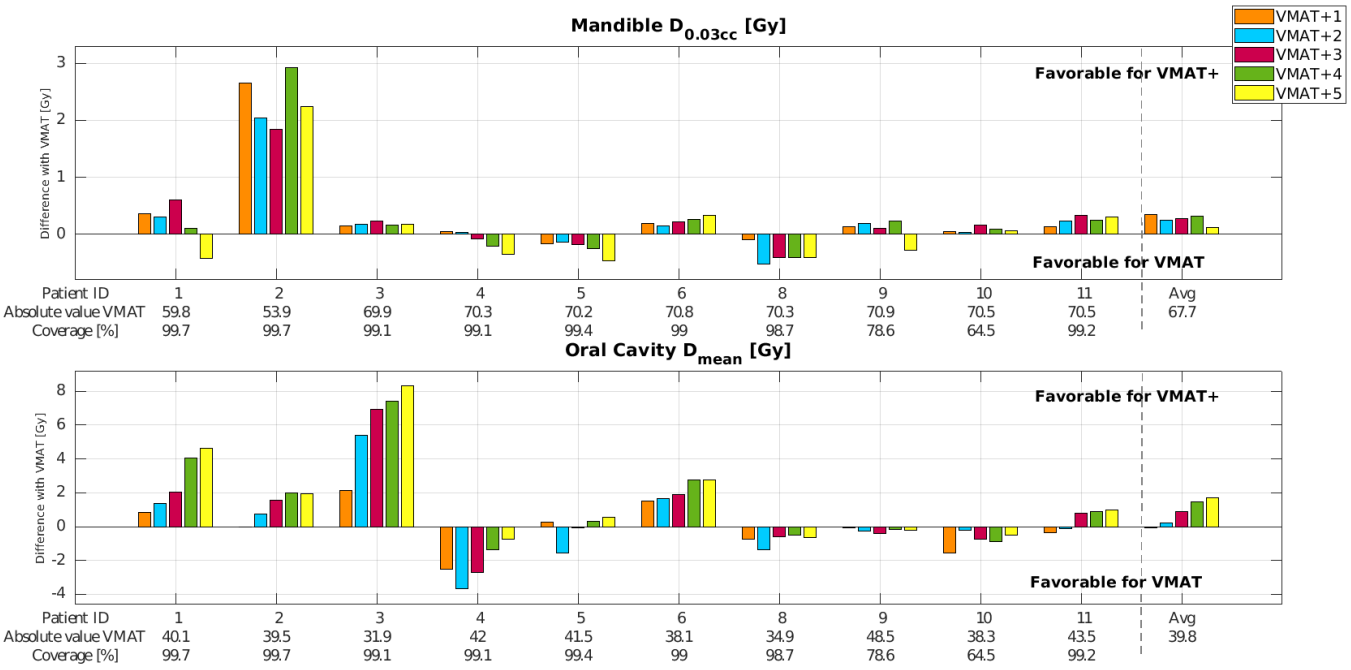
(c)


Cochlea R D mean [Gy]
VMAT+1
VMAT+2
VMAT+3
VMAT+4
VMAT+5
Favorable for VMAT+
Favorable for VMAT
Difference with VMAT [Gy]
Patient ID 1 2 3 4 5 6 8 9 10 11 Avg
Absolute value VMAT 39.8 34.9 20 35 35.4 20.7 35.1 55.7 52.7 55.3 38.5
Coverage [%] 99.7 99.7 99.1 99.1 99.4 99 98.7 78.6 64.5 99.2
Cochlea L D mean [Gy]
Favorable for VMAT+
Favorable for VMAT
Difference with VMAT [Gy]
Patient ID 1 2 3 4 5 6 8 9 10 11 Avg
Absolute value VMAT 35.2 34.7 34.7 35 35 34.7 35.1 57.6 55.2 60.6 41.8
Coverage [%] 99.7 99.7 99.1 99.1 99.4 99 98.7 78.6 64.5 99.2

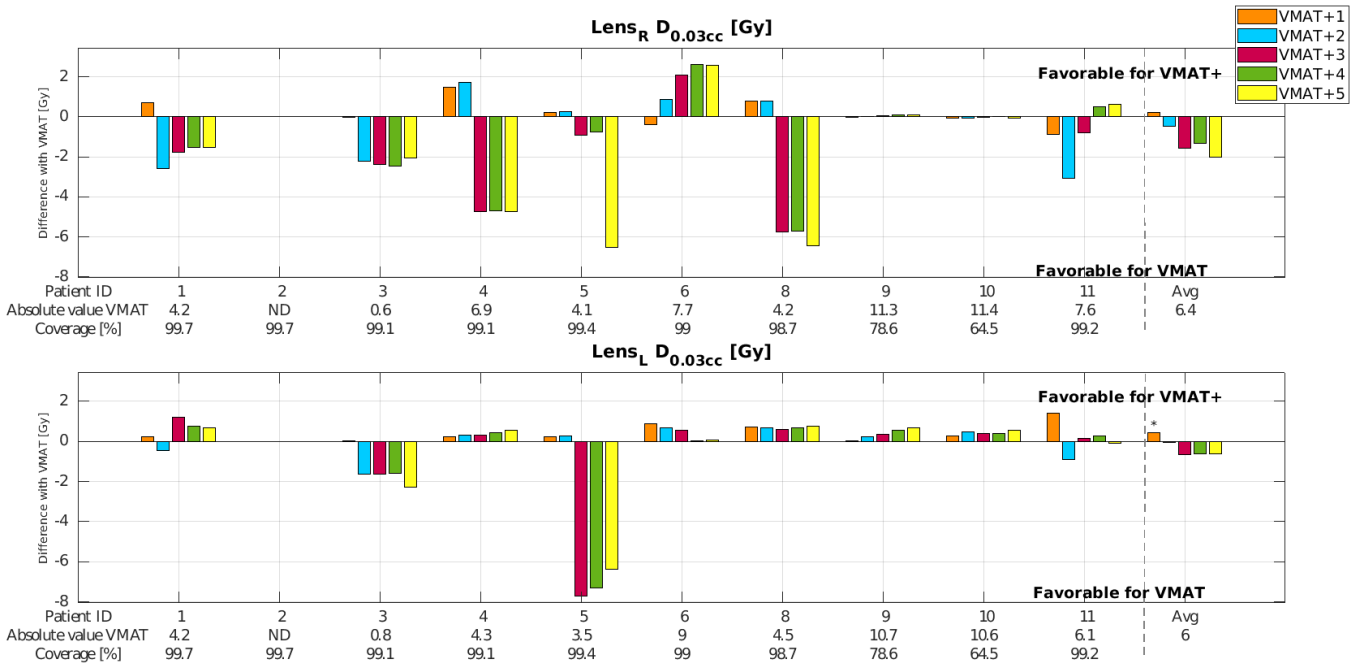
(d)


Superior SwM D mean [Gy]
Middle SwM D mean [Gy]
Inferior SwM D mean [Gy]
VMAT+1
VMAT+2
VMAT+3
VMAT+4
VMAT+5
Favorable for VMAT+
Favorable for VMAT
Difference with VMAT [Gy]
Patient ID
Absolute value VMAT
Coverage [%]
1 2 3 4 5 6 8 9 10 11 Avg
64.8 61.1 53.3 67.3 58.9 57.1 61 67.1 64.9 70.8 62.6
99.7 99.7 99.1 99.1 99.4 99 98.7 78.6 64.5 99.2
56.1 50.2 25.3 45.8 42 39.1 52.8 60.4 56.3 70.8 49.9
99.7 99.7 99.1 99.1 99.4 99 98.7 78.6 64.5 99.2
25.2 29.8 2.6 25.1 25 28.7 41.2 36 48.3 55.8 31.8
99.7 99.7 99.1 99.1 99.4 99 98.7 78.6 64.5 99.2

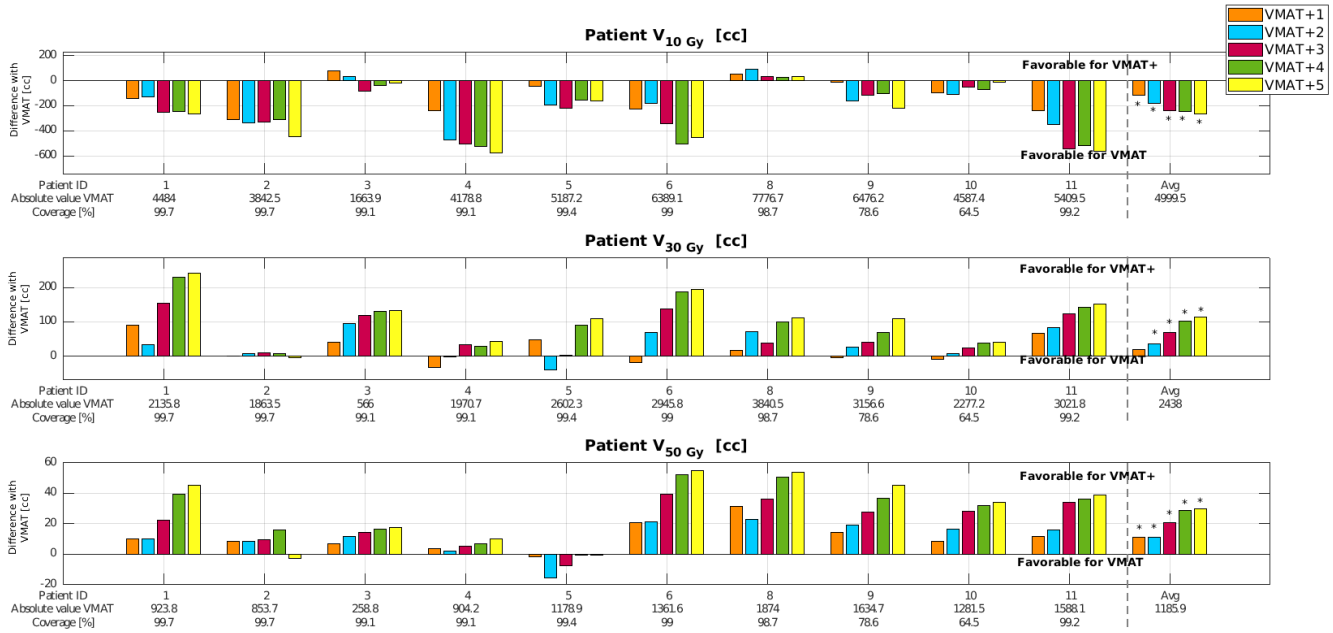
(e)


Mandible D 0.03cc [Gy]
Oral Cavity D mean [Gy]
VMAT+1
VMAT+2
VMAT+3
VMAT+4
VMAT+5
Favorable for VMAT+
Favorable for VMAT
Difference with VMAT [Gy]
Patient ID
Absolute value VMAT
Coverage [%]
1 2 3 4 5 6 8 9 10 11 Avg
59.8 53.9 69.9 70.3 70.2 70.8 70.3 70.9 70.5 70.5 67.7
99.7 99.7 99.1 99.1 99.4 99 98.7 78.6 64.5 99.2
40.1 39.5 31.9 42 41.5 38.1 34.9 48.5 38.3 43.5 39.8
99.7 99.7 99.1 99.1 99.4 99 98.7 78.6 64.5 99.2

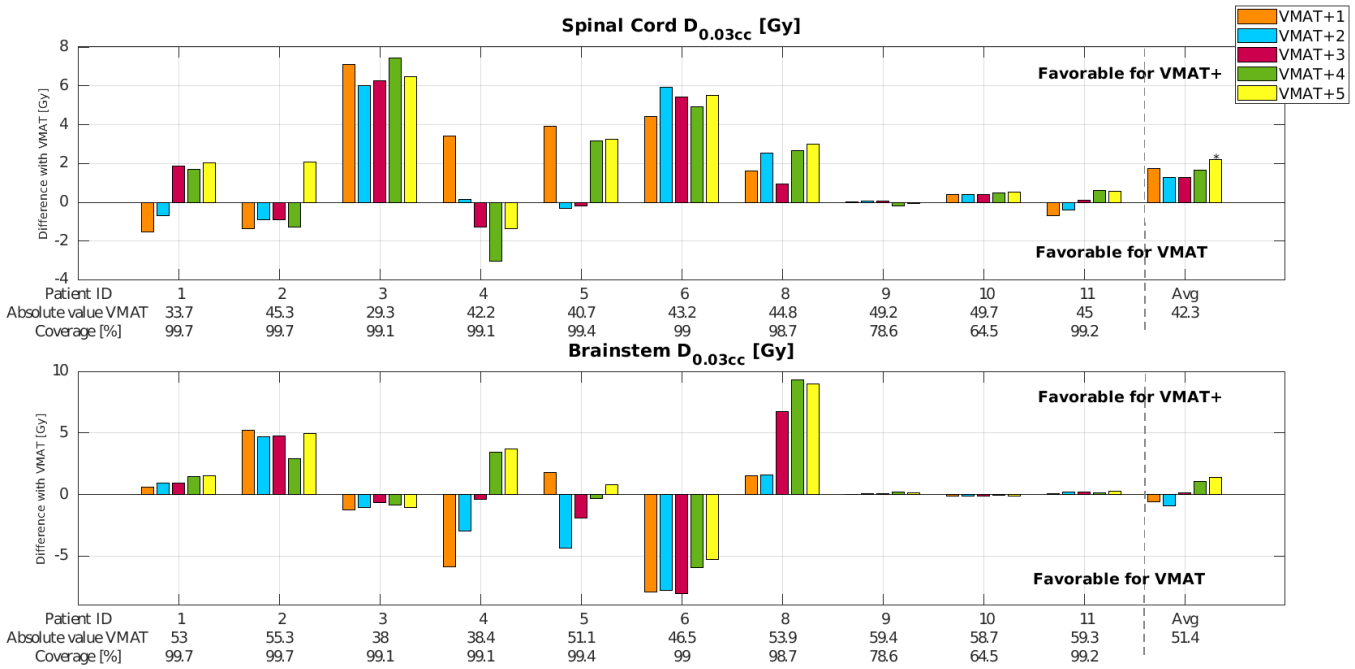
(f)


Lens$_R$ $D_{0.03cc}$ [Gy]
VMAT+1
VMAT+2
VMAT+3
VMAT+4
VMAT+5
Favorable for VMAT+
Favorable for VMAT
Difference with VMAT [Gy]
Patient ID 1 2 3 4 5 6 8 9 10 11 Avg
Absolute value VMAT 4.2 ND 0.6 6.9 4.1 7.7 4.2 11.3 11.4 7.6 6.4
Coverage [%] 99.7 99.7 99.1 99.1 99.4 99 98.7 78.6 64.5 99.2
Lens$_L$ $D_{0.03cc}$ [Gy]
Favorable for VMAT+
Favorable for VMAT
Difference with VMAT [Gy]
Patient ID 1 2 3 4 5 6 8 9 10 11 Avg
Absolute value VMAT 4.2 ND 0.8 4.3 3.5 9 4.5 10.7 10.6 6.1 6
Coverage [%] 99.7 99.7 99.1 99.1 99.4 99 98.7 78.6 64.5 99.2

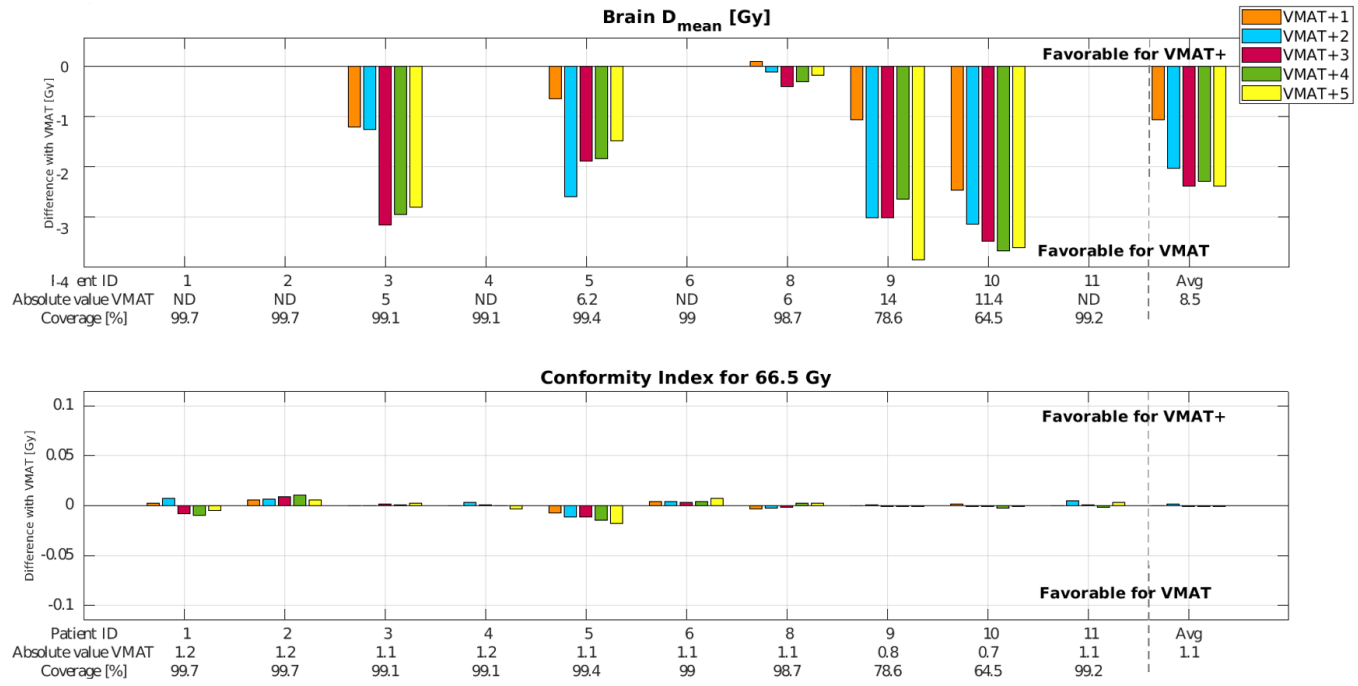
(g)


Patient $V_{10\ Gy}$ [cc]
VMAT+1
VMAT+2
VMAT+3
VMAT+4
VMAT+5
Favorable for VMAT+
Favorable for VMAT
Difference with VMAT [cc]
Patient ID 1 2 3 4 5 6 8 9 10 11 Avg
Absolute value VMAT 4484 3842.5 1663.9 4178.8 5187.2 6389.1 7776.7 6476.2 4587.4 5409.5 4999.5
Coverage [%] 99.7 99.7 99.1 99.1 99.4 99 98.7 78.6 64.5 99.2
Patient $V_{30\ Gy}$ [cc]
Favorable for VMAT+
Favorable for VMAT
Difference with VMAT [cc]
Patient ID 1 2 3 4 5 6 8 9 10 11 Avg
Absolute value VMAT 2135.8 1863.5 566 1970.7 2602.3 2945.8 3840.5 3156.6 2277.2 3021.8 2438
Coverage [%] 99.7 99.7 99.1 99.1 99.4 99 98.7 78.6 64.5 99.2
Patient $V_{50\ Gy}$ [cc]
Favorable for VMAT+
Favorable for VMAT
Difference with VMAT [cc]
Patient ID 1 2 3 4 5 6 8 9 10 11 Avg
Absolute value VMAT 923.8 853.7 258.8 904.2 1178.9 1361.6 1874 1634.7 1281.5 1588.1 1185.9
Coverage [%] 99.7 99.7 99.1 99.1 99.4 99 98.7 78.6 64.5 99.2

(h)



(i)



(j)

Figure 3.3: Comparisons of VMAT+ plan parameters with VMAT for a) right and left parotids D_{mean}, b) right and left submandibular glands D_{mean}, c) larynx and esophagus D_{mean}, d) right and left cochleas D_{mean}, e) superior, middle and inferior swallowing muscles D_{mean}, f) mandible $D_{0.03\,cc}$ and oral cavity D_{mean}, g) right and left lenses D_{mean}, h) patient $V_{10\,Gy}$, $V_{30\,Gy}$ and $V_{50\,Gy}$, i) spinal cord and brainstem $D_{0.03\,cc}$ and j) PTV70 CI for 66.5 Gy (95% of the prescribed dose) and brain D_{mean}. Positive is favorable for VMAT+; Negative is favorable for VMAT. VMAT values for each parameter and PTV70 coverage ($V_{95\%}$) for each patient are reported below the patient ID. * points at statistically significant differences with VMAT. For the brain it was not to possible to calculate statistical significance as the sample size was too small [12]. ND=Non delineated OAR. Patients were ordered according to increasing PTV70 volume.

3.2.3.3 Analysis for a selected patient

Performance of the various beam configurations depended on the considered OAR and patient. In this section, one patient will be analyzed in some detail. Only VMAT, VMAT+1, VMAT+3 and VMAT+5 are compared to show the variation between different number of beams for VMAT+.

Patient 3

Patient 3 has a small tumor on the left, as represented in figure 3.1.

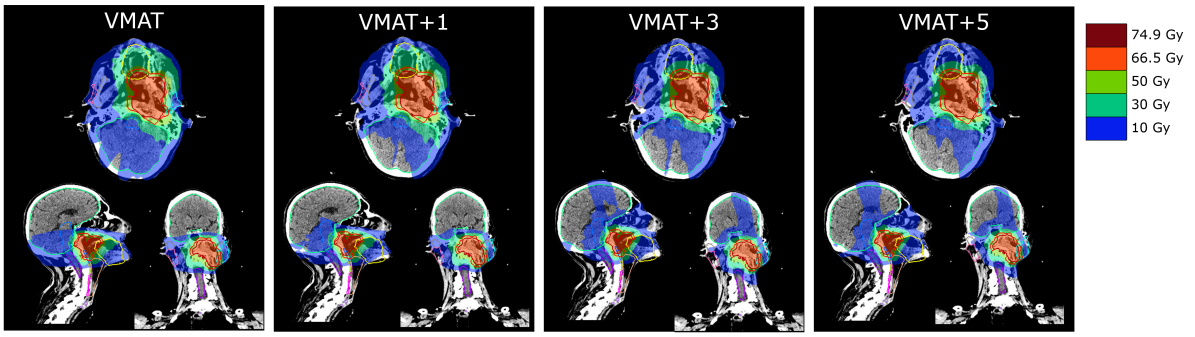


Figure 3.4: Dose distributions for patient 3. PTV70 delineated in red. Left parotid delineated in bright blue, right parotid in pink, right SMG in bright blue, left SMG in dark blue, superior SwM in blue, middle SwM in green, inferior SwM in pink, oral cavity in yellow, mandible in brown and spinal cord in dark red.

For this patient, VMAT+ plans are better for most plan parameters. There are large improvements with VMAT+3, VMAT+4 and VMAT+5, compared to VMAT, for both parotids (at least 3 Gy less than VMAT), the right cochlea (at least 2.5 Gy less than VMAT) and oral cavity (at least 6 Gy less than VMAT), see figure 3.3a, 3.3d and 3.3f. Spinal cord $D_{0.03\,cc}$ is reduced by at least 6 Gy with all VMAT+ plans (figure 3.3i).

VMAT performs better for the inferior SwM and the lenses, but for the three organs, the resulting doses with VMAT+ are far from the dose restrictions. I.e., for the inferior SwM the plan with the highest D_{mean} is the VMAT+3, receiving 4.6 Gy, for the right lens VMAT+4 $D_{0.03\,cc}$ is 2.6 Gy and for the left lens VMAT+5 $D_{0.03\,cc}$ is 2.8 Gy, figure 3.3e and 3.3g.

The only parameter where VMAT may be better than VMAT+ plans is for the brain, as for VMAT+3, VMAT+4 and VMAT+5 have higher brain mean doses (see figure 3.3j and 3.4).

3.2.4 Subjective plan selection by observers

Results of subjective plan selections by reviewers are presented in figure 3.5. Figure 3.5a shows the best and second best plans according to reviewers A to D considering plan quality only, while plan selection based on quality and delivery time is presented in figure 3.5b.

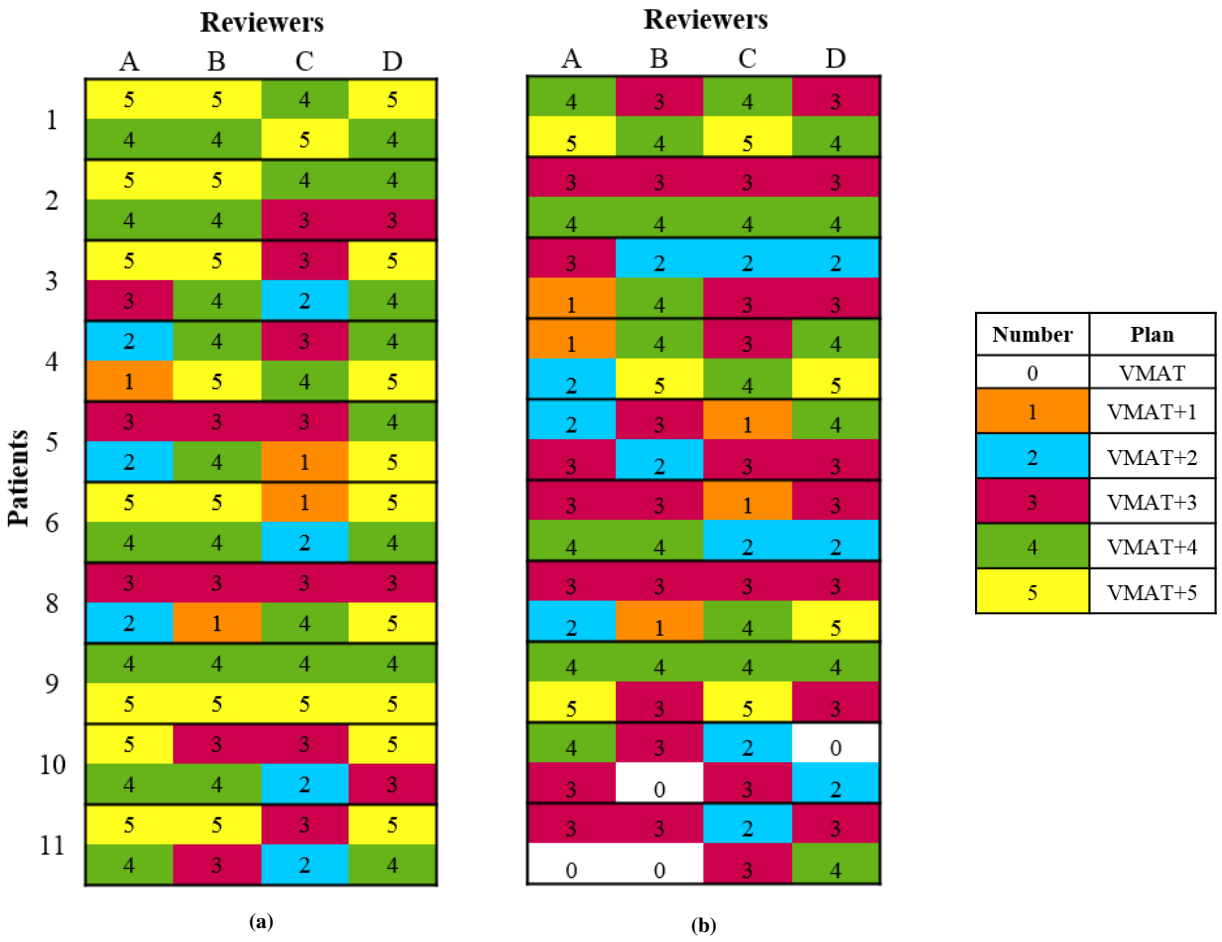


Figure 3.5: Plans chosen by each reviewer considering a) plan quality and b) plan quality and delivery time. Each reviewer chose the best and second best plan for each patient, e.g. for patient 1, reviewer A chose as best plan VMAT+5 and as second best VMAT+4 when only considering plan quality.

When performing plan selection based on plan quality only, the most selected plan as first option was VMAT+5 and for second option it was VMAT+4, as seen in figure 3.6a. VMAT was never chosen. VMAT+1 and VMAT+2 were rarely selected and usually as the second best.

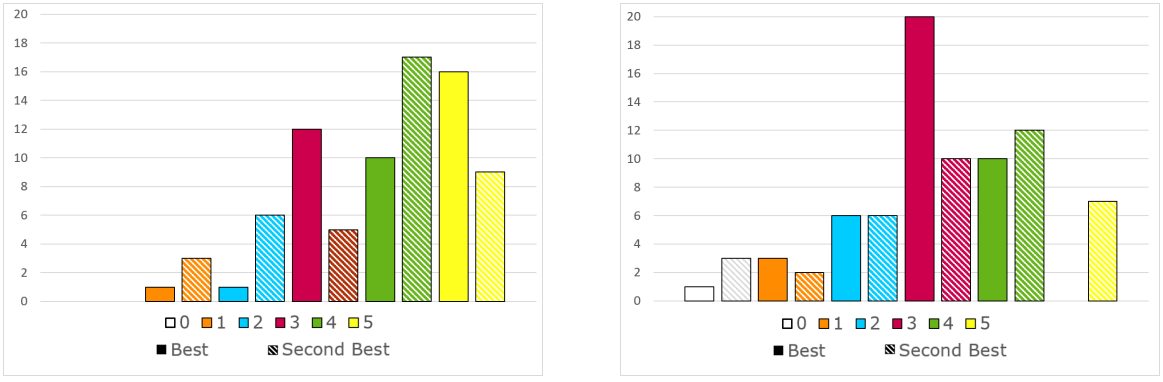


Figure 3.6: Frequency with which plans were selected as best and second best option when considering a) plan quality and b) plan quality and delivery time. Solid bars report plans selected as best; dashed bars report plans selected as second best.

Considering plan quality and delivery time, VMAT+3 was selected the most as first option and VMAT+4 was selected the most as second option (figure 3.6b). VMAT+5 was never selected as the best option. VMAT was selected more often as second option than as first option.

Figure 3.7 shows frequency distributions for best and second best plans together, again showing that when delivery time is considered as well, the optimal number of beams reduces.

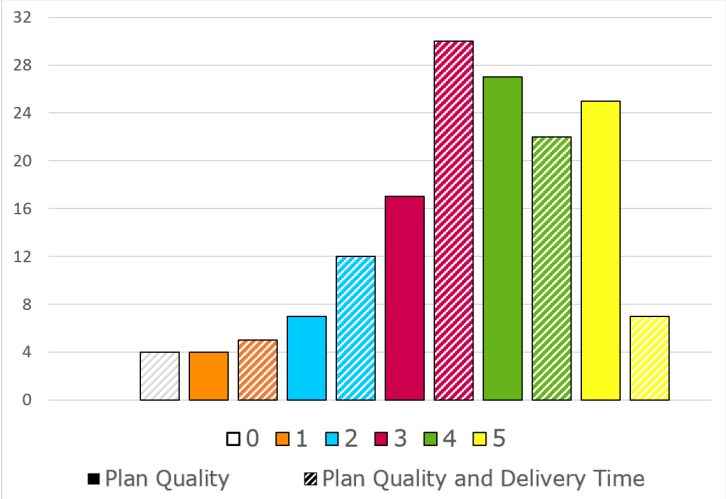


Figure 3.7: Frequency with which plans were selected as best or second best plan. Solid bars report plan selection based on only plan quality; dashed bars report plan selection based on plan quality and delivery time.

Figure 3.8 represents the frequency with which each plan was selected as the best one by at least 3 reviewers, considering plan quality and plan quality and delivery time. Mostly VMAT+ plans with more than 3 beams were considered the best plans (figure 3.8). VMAT+5 was only chosen as the best plan when delivery time was not considered. VMAT+3 was most often chosen when plan quality and delivery time were both considered. VMAT+4 was selected (almost) equally for both plan selections.

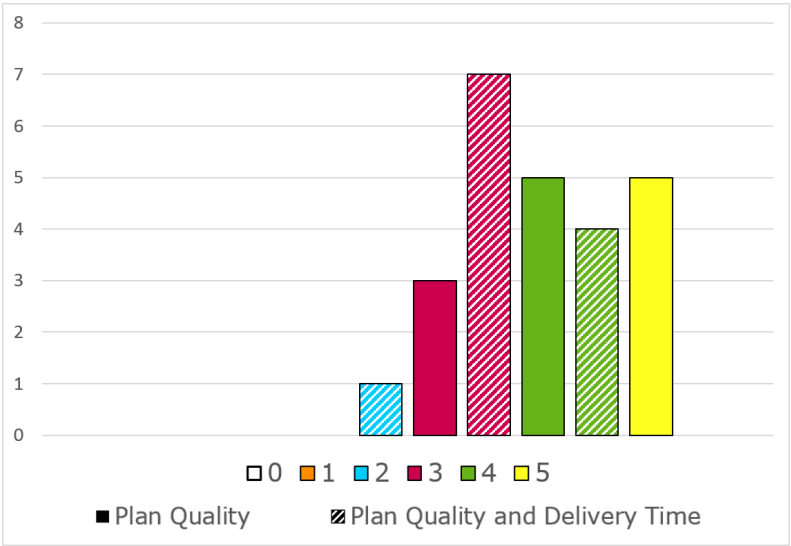


Figure 3.8: Frequency of plan selected as either first or second option, unanimously by at least 3 reviewers. Solid bars report plan selection based on only plan quality; dashed bars report plan selection based on plan quality and delivery time.

3.2.5 Weight of non-coplanar beams in VMAT+5 plans

For VMAT+5 plans, most of the weight for PTV Dmean comes from VMAT (see figure 3.9), but with considerable, patient-dependent contributions of the non-coplanar IMRT beams. The contribution of the added beams was on average 33.5%, with a minimum of 19.7% and a maximum of 54.3%.

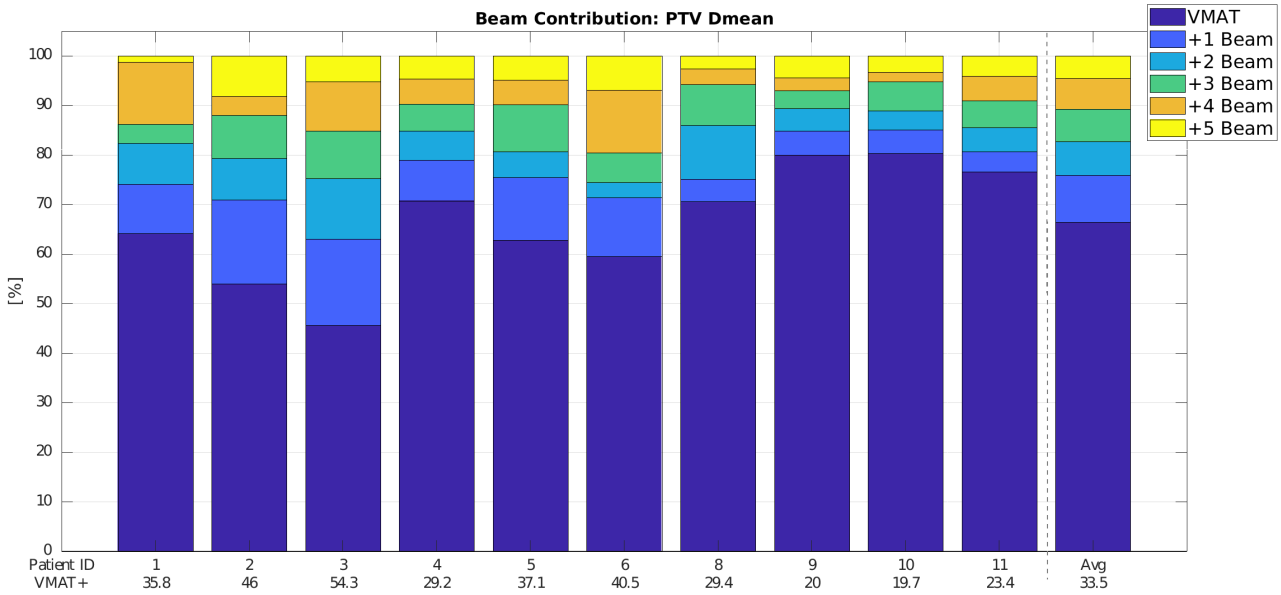


Figure 3.9: Contributions to PTV D_{mean} from VMAT (dark blue) and added non-coplanar beams (+1 to +5). For each patient, the total contribution of the non-coplanar beams is indicated along the x-axis, below patient number

3.3 Discussion

In this study, we have used automated plan generation to investigate the value of added patient-optimized non-coplanar IMRT beams to VMAT for nasopharyngeal carcinoma. The first step was to create a wish-list that allows for better or similar plans as those manually created and clinically applied. In the next step, it was demonstrated for VMAT that the quality of not-translated Erasmus-iCycle plans was highly similar to translated plans. This observation was the basis for the decision to use not-translated VMAT and VMAT+ for the major topic of the research, i.e. assessment of the values of VMAT+ compared to VMAT.

Overall, VMAT+ plans outperformed VMAT regarding plan quality. The superiority of VMAT+ plans over VMAT, reconfirms the benefit of non-coplanar irradiation for NPC, as indicated by Wild et al. [4]. Observed overall plan quality increases were: reduced D_{mean} for structures important for salivary production, i.e. the parotids, submandibular glands and oral cavity (although the latter two were not statistically significant); reduced patient $V_{30\,Gy}$ and $V_{50\,Gy}$; and reduced $D_{0.03\,cc}$ for the spinal cord, which was also found for hybrid plans by Akbas et al. [36]. Probably, the parotids showed most sparing through VMAT+ plans because they were the highest priority OAR, so the enhanced degree of freedom for generating plans was first and predominantly used to reduce parotid doses.

Apart from the parotids, sparing for the other of the OARs was highly patient and OAR-dependent. For some patients, already one optimized beam improved OAR sparing. There are also large variations in the potential clinical relevance of observed differences between VMAT and VMAT+.

VMAT+ is overall worse for lower patient doses, i.e. patient $V_{10\,Gy}$ is worse. The lenses and the brain generally declined with VMAT+. This is probably related to the low priority of both of these OARs.

Patient anatomy is decisive in the sparing process. Patients whose tumor is further away from specific OARs may benefit more from added non-coplanar beams to the coplanar VMAT, without significantly compromising the other OARs. For example, for patients with small unilateral tumor, the dose in the oral cavity was always reduced, with limited increase for the other organs, as for the esophagus, and the inferior swallowing muscle.

Delivery time may be decisive when selecting the plan, as reflected in the plan selections. With more added beams, treatments are longer, so VMAT+5 treatments can be more than 3 times longer than VMAT treatments. VMAT+3 and VMAT+4 were selected more than less time-consuming plans, both when considering plan quality only and plan quality and delivery time. Furthermore, VMAT+3 and VMAT+4 were considered the best plans most often, reflecting that the longer delivery time is justifiable because of the higher plan quality of added non-coplanar beams.

VMAT+ plans are considerably more time-consuming than VMAT plans, but, considering the patient-dependence of improvements for most of the OARs, a prospective generation of VMAT and VMAT+ plans would allow physicians to select the best dose distribution for each patient.

The 5 patient-optimized beams in VMAT+5 were relevant to PTV D_{mean} contribution.

In this study, only VMAT+ was investigated for 10 patients treated for NPC, with varied tumor presentations. In order to have more firm and significant conclusions, VMAT+ needs to be investigated for a larger patient cohort.

3.4 Conclusions

Automated VMAT treatment planning was performed for nasopharyngeal carcinoma. Quality of automatically generated VMAT plans is higher than that of the clinically applied, manually generated plans. Overall, plan quality improved when providing VMAT with computer-optimized non-coplanar IMRT beams, with large variations in plan parameters and among patients. When considering treatment delivery time, VMAT+3 and VMAT+4 were the most selected plans. In particular, VMAT+3 was found to be the most appropriate treatment, reflecting that longer treatment plans may be justifiable for this treatment site. Automated treatment planning allows for prospective plan generation, which would allow the optimal plan selection.

4 Mediastinal lymphoma

4.1 Material and Methods

4.1.1 Patients

In this study, contoured CT scans of 25 previously treated mediastinal lymphoma patients were used (21 Hodgkin lymphoma and 4 B cell non-Hodgkin lymphoma).

Disease presentation was very heterogeneous, involving any combination of superior/inferior mediastinum, with/without supraclavicular or axillar nodes involvement, bulky disease or complex anatomy (see figure 4.1). Median PTV volume was 605 ± 410 cc (range: 86-585 cc). The prescribed dose was 30 Gy, delivered in 15 fractions.

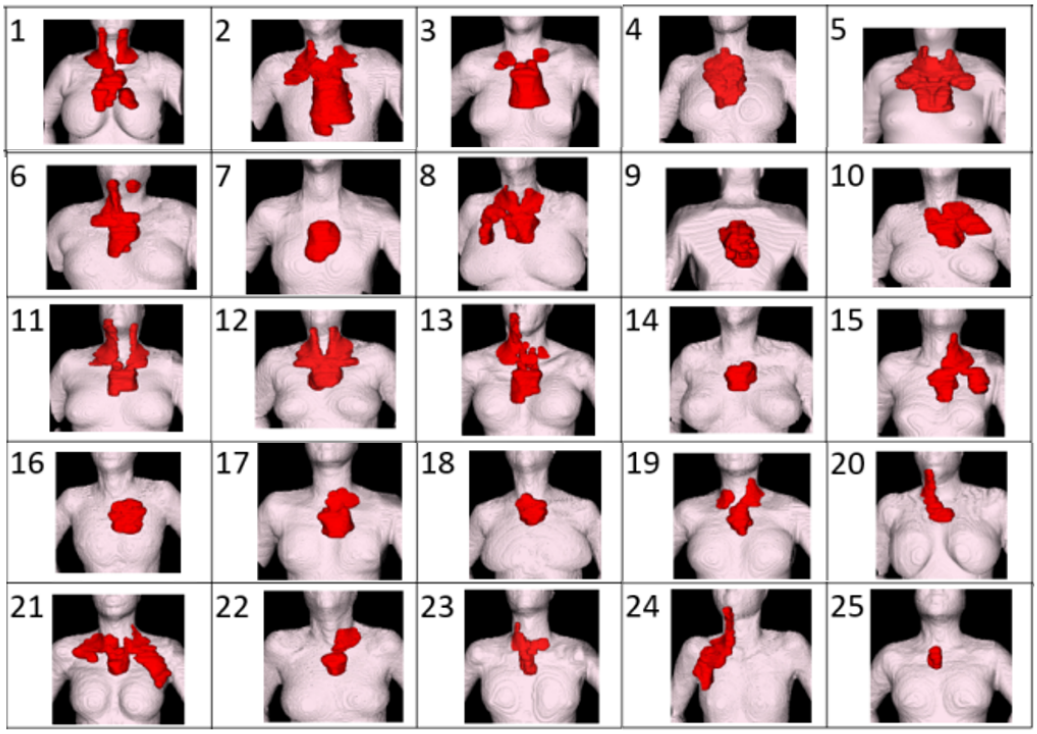


Figure 4.1: Study patients ordered according to decreasing heart D_{mean} as reported in [11].

4.1.2 Clinical protocol

In the clinical planning protocol a list of requirements for the target dose and OAR doses are defined, briefly reported here. The PTV coverage, i.e. the volume of the target that receive 95% of the prescribed dose, had to be at least 95% (PTV $V_{95\%} > 95\%$). Dose in the PTV had also to respect over- and under-dose limits: $V_{110\%} < 1\%$ and $V_{< 90\%} < 5$ cc, i.e. the volume receiving less than 90% of the prescribed dose should be less than 5 cc (preferably < 2 cc).

For the OARs, there was a maximum accepted value and an aim (the latter stated in parenthesis when available): breasts $D_{mean} < 5$ Gy (< 2 Gy), heart $D_{mean} < 26$ Gy (< 20 Gy), lungs $D_{mean} < 15$ Gy (< 13.5 Gy), $V_{5\,Gy} < 55\%$ ($< 50\%$) and $V_{20\,Gy} < 20\%$. These OAR requirements were not hard constraints and higher values were accepted in favor of acceptable PTV coverage (=95%). Clinically, the 60% isodose was (visually) evaluated to check that dose was not entering to much in the back and neck muscles.

4.1.3 Automated plan generation

All plans were generated with Erasmus-iCycle, with the same wish-list. This wish-list was developed in a process similar to what was described in section 3.1.3 and by Rossi and Cambraia Lopes, et al. [11].

Table 4.1 shows the used wish-list, with constraints and objectives in the upper and lower panels, respectively. Constraints limit over- and mean dosage for PTV, breasts D_{mean}, dose fall off from 0.3 to 5 cm from the PTV, and entrance dose (i.e. dose in the first 2 cm below the patient skin).

Objective optimization starts with PTV coverage optimization, followed by PTV D_{min} maximization. Priorities 3 and 4 are meant to conform the dose bath. In the following priorities, EUDs and D_{mean} cost functions were used to control dose in the breast, lungs and heart. EUDs with k=0.5 were used to control low-dose bath in lungs and breast. As the last priority, a shell at 1 cm from the PTV is used to minimize dose outside the PTV.

Table 4.1: Wish-list used in autoplanning for all ML patients. [a] dose in first 2 cm inwards the patient contour, subtracting PTV expanded by 7 cm. [b] PTV expanded by 0.5 cm, equivalent for the other rings. [c] Patient contour - PTV expanded by 5 cm.

Constraints

Structure	Type	Limit
PTV	maximum	32.1 Gy
PTV	mean	30.6 Gy
Breast L	mean	5 Gy
Breast R	mean	5 Gy
Shell 0.3 cm from PTV	maximum	30 Gy
Shell 1 cm from PTV	maximum	28.5 Gy
Shell 3 cm from PTV	maximum	27 Gy
Shell 5 cm from PTV	maximum	22.5 Gy
Entrance dose [a]	maximum	18 Gy

Objectives

Priority	Structure	Type	Goal	Sufficient	Parameters
1	PTV	LTCP	0.2	0.2	D_l=28.5 Gy, α=0.8
2	PTV	minimum	28.5 Gy		
3	Ring 2 cm around PTV [b]	maximum	28.5 Gy		
4	Patient - PTV exp 5 cm [c]	maximum	21 Gy		
5	Lungs - PTV	EUD	6 Gy	6 Gy	k=0.5
6	Lungs - PTV	EUD	22 Gy	22 Gy	k=8
7	Breast L	EUD	0.9 Gy		k=0.5
7	Breast R	EUD	0.9 Gy		k=0.5
8	Heart - PTV	mean	0 Gy		
9	Lungs - PTV	mean	0 Gy		
10	Heart - PTV	EUD	0 Gy		k=8
11	Breast L	EUD	0 Gy		k=8
11	Breast R	EUD	0 Gy		k=8
12	Shell 1 cm from PTV	maximum	27 Gy		

4.1.3.1 Generated plans for plan comparisons and evaluations

Erasmus-iCycle was used to automatically generate 7 plans per patient:

1. VMAT, 23 equiangular coplanar IMRT beams, used for all patients;
2. FaB-VMAT, one arc of 23 equiangular coplanar IMRT beams and a 6 equiangular non-coplanar IMRT beams partial arc, mimicking a non-coplanar perpendicular 60 ^{o} partial arc, used for all patients;
3. 5 VMAT+ plans, as VMAT+1, VMAT+2, VMAT+3, VMAT+4 and VMAT+5.

For VMAT+ plans, first a coplanar VMAT was simulated with 23 equi-angular IMRT beams; afterwards, the optimal non-coplanar beam was sequentially added generating plans with 1, 2, 3, 4 or 5 patient-specific non-coplanar IMRT beams, using BAO, as explained in section 2.3.

Compared to previous research in [11], there were some minor simplifications to the BAO search space to make calculations times feasible. The applied beam energy was 6 MV and a Monte Carlo dose engine was used, to account for the air cavities in the lungs, as in [11].

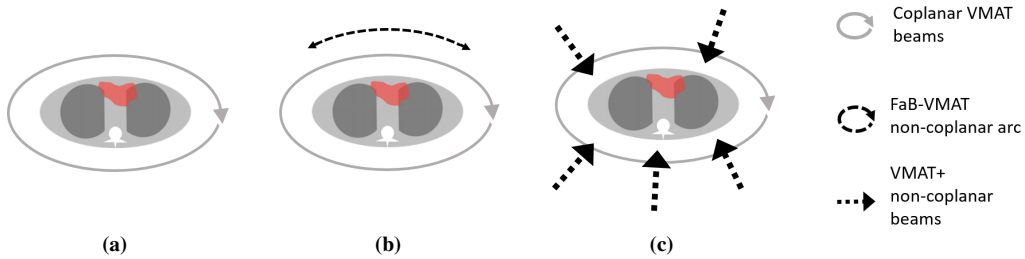


Figure 4.2: Schematic presentation of the investigated beam configurations. a) coplanar VMAT b) Full-arc butterfly VMAT (FaB-VMAT) c) VMAT with 5 optimized non-coplanar beams (VMAT+5). Adapted from [11]

4.1.4 Plan comparisons and evaluations

For plan comparisons, plans were first rescaled to the lowest PTV coverage of the compared plans. This method minimized bias related to PTV coverage when comparing OARs doses in different plans.

Plan evaluation and comparison focused on dosimetric comparisons and dose distributions, using PTV and OAR planning goals as applied in clinical practice. For the PTV, coverage for 95% of the volume ($V_{95\%}$ [%]), overdose volumes ($V_{107\%}$ [%]), under-dose volumes ($V_{<90\%}$ [cc]), and the conformity index (CI, defined as patient $V_{95\%}$ / V_{PTV}) were evaluated. For OARs, D_{mean} and $V_{4\,Gy}$ [%] were evaluated for breasts, D_{mean}, $V_{5\,Gy}$ [%] and $V_{20\,Gy}$ [%] for lungs, D_{mean} for heart. Patient irradiation was evaluated using $V_{5\,Gy}$ [%] and $V_{20\,Gy}$ [%], respectively.

Statistical analyses were performed with two-sided Wilcoxon signed-rank tests. Differences with p-value < 0.05 were considered statistically significant.

4.1.5 Subjective treatment plan selection

To further evaluate the different beam configurations, 4 reviewers were asked to independently compare and choose the best and second best plans for each of the 25 patients, out of all 7 options (i.e. VMAT, FaB-VMAT, and VMAT+1 to VMAT+5). Reviewers had access to breasts D_{mean} and $V_{4\,Gy}$, heart D_{mean}, lungs D_{mean}, $V_{5\,Gy}$ and $V_{20\,Gy}$, patient $V_{5\,Gy}$ and $V_{20\,Gy}$, and estimated delivery time (table 4.2), with PTV doses comparable between plans and therefore omitted.

Plan selection was performed twice: 1) considering only the plan quality and 2) considering the plan quality and delivery time. Treatment delivery times are presented in table 4.2. Times were estimated based on previous research by Sharfo et al. [41], as described in section 3.1.5. For FaB-VMAT, the presented time encompasses the time for radiation delivery and to move the couch.

Plan selection was analyzed by how many times a plan was chosen, as first and second option separately (for both performed plan selections, i.e. considering or not delivery time) and what plans were chosen the most. With the latter, a plan was considered "the best" when at least 3 reviewers chose it as either first or second option. This last approach was used in order to investigate if there was consensus between the reviewers.

Plan	**VMAT**	**VMAT+1**	**VMAT+2**	**VMAT+3**	**VMAT+4**	**VMAT+5**	**FaB-VMAT**
Time (min)	3	4.5	6	7.5	9	10.5	5

Table 4.2: Table with estimated VMAT, VMAT+ an FaB-VMAT treatment times.

4.1.6 Weight of non-coplanar beams in VMAT+5 plans

Each beam in a treatment plan contributes to the PTV D_{mean}. For each of the 25 VMAT+5 plans, the contribution to PTV D_{mean} of the coplanar VMAT and the added beams was analyzed.

4.2 Results

4.2.1 Quality of generated plans

All 175 automatically generated treatment plans were considered clinically acceptable. More in details, all plans satisfied PTV coverage 95% and under- and over-dosage requirements. For the OARs, 154 out of the 175 plans had OAR dosimetrical parameters below (the strict) requirements reported in the clinical protocol (see section 4.1.2). All generated plans for patients 1, 2 and 5 had a lungs $V_{5\,Gy} > 55\%$, which was also observed and accepted in the clinical treatment in [11].

4.2.2 Dosimetrical comparisons of VMAT, FaB-VMAT and VMAT+ plans

All 175 plans showed highly comparable PTV doses after rescaling to 99% coverage, the minimum obtained coverage among all generated plans, with similar under- and over-dose spots, as seen in figure E.1b and E.1c, respectively. Therefore, the main focus of plan comparisons will be OAR and patient doses.

Averages, standard deviations and ranges for differences between VMAT and VMAT+ and FaB-VMAT plans are in appendix D, table D.1 and D.2. Average differences between all plans and corresponding p-values for all considered plan parameters are reported in appendix E. Figure 4.3 compares dose distributions for an example patient. Comparisons between VMAT, VMAT+ and FaB-VMAT plan parameters for individual patients are presented in figure 4.4.

This section is now divided in 4 parts. First, the average results based on all patients and OARs will be presented for 1) the comparison VMAT+ and FaB-VMAT vs. VMAT, and 2) the comparison FaB-VMAT vs VMAT+. Then, 3) an analysis for each separate OAR, for all beam configurations and patients, will be presented and, as last, 4) an analysis of one selected patient.

4.2.2.1 Population analysis: VMAT+ and FaB-VMAT vs. VMAT

- Although not always statistically significant and probably also not always clinically relevant, VMAT+ and FaB-VMAT had generally lower population average values than VMAT for most investigated plan parameters, i.e. for breast, heart, and lungs D_{mean}, lungs $V_{5\,Gy}$ and $V_{20\,Gy}$, patient $V_{5\,Gy}$ and $V_{20\,Gy}$, and conformity index (see figure 4.4a, and 4.4c to 4.4i). Only for breasts $V_{4\,Gy}$ the differences were less apparent (figure 4.4b). For most parameters with advantages for VMAT+, the advantage was seen for (almost) all patients.

- VMAT+5 and FaB-VMAT were overall superior to VMAT (see figure 4.4a to 4.4i), with differences statistically significant for all parameters except breasts $V_{4\,Gy}$ (see figure 4.4b and table D.2). On average, differences were considered clinically relevant for heart D_{mean} and lungs D_{mean} and $V_{5\,Gy}$, even if moderate (reductions with VMAT+5: 0.6 ± 0.5 Gy, 0.6 ± 0.5 Gy and $3.8 \pm 3.6\%$, respectively, all $p < 0.001$). VMAT+5 and FaB-VMAT could also reduce the spread of dose in the patient as clearly visible in figure 4.3 for an example patient, and in figure 4.4g, 4.4h and 4.4i for the patient population.

- Differences between VMAT+ plans with consecutive number of beams, i.e. VMAT+1 and VMAT+2, and VMAT+2 and VMAT+3, were usually very limited. Improvements between plans were generally statistically significant for lungs D_{mean}, $V_{5\,Gy}$ and $V_{20\,Gy}$, and patient $V_{5\,Gy}$ and $V_{20\,Gy}$ (figure E.1h to E.1l). On average VMAT+5 was the best for all the OARs, except the breasts (see figure 4.4a and 4.4b), but improvements were only statistically significant for lungs D_{mean}, $V_{5\,Gy}$ and $V_{20\,Gy}$ (figure E.1h to E.1j).

- For most plan parameters, differences between VMAT and VMAT+ and between VMAT and FaB-VMAT were highly patient dependent, as in figure 4.4.

4.2.2.2 Population analysis: VMAT+ vs FaB-VMAT

- For most plan parameters, VMAT+4 and VMAT+5 were superior to FaB-VMAT, although not always statistically significant, and probably the differences were often also not of high clinical relevance (figure 4.4 and E.1).

- Only for breasts D_{mean} and $V_{4\,Gy}$, FaB-VMAT was superior to VMAT+4 and VMAT+5, but differences were small and not statistically significant (figure 4.4a, 4.4b, E.1e and E.1f).

- Superiority of VMAT+4 and especially VMAT+5 in plan parameter values compared for FaB-VMAT was seen for most patients, but there were exceptions (figure 4.4).

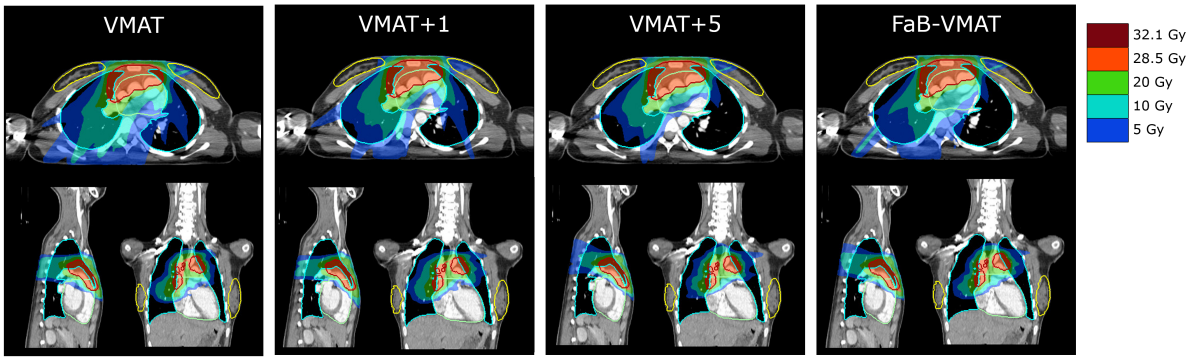


Figure 4.3: Dose distributions for patient 7, in axial (superior), sagittal (left) and coronal (right) views. PTV delineated in red, breasts delineated in yellow, lungs in blue and heart in green.

4.2.2.3 Per OAR analysis

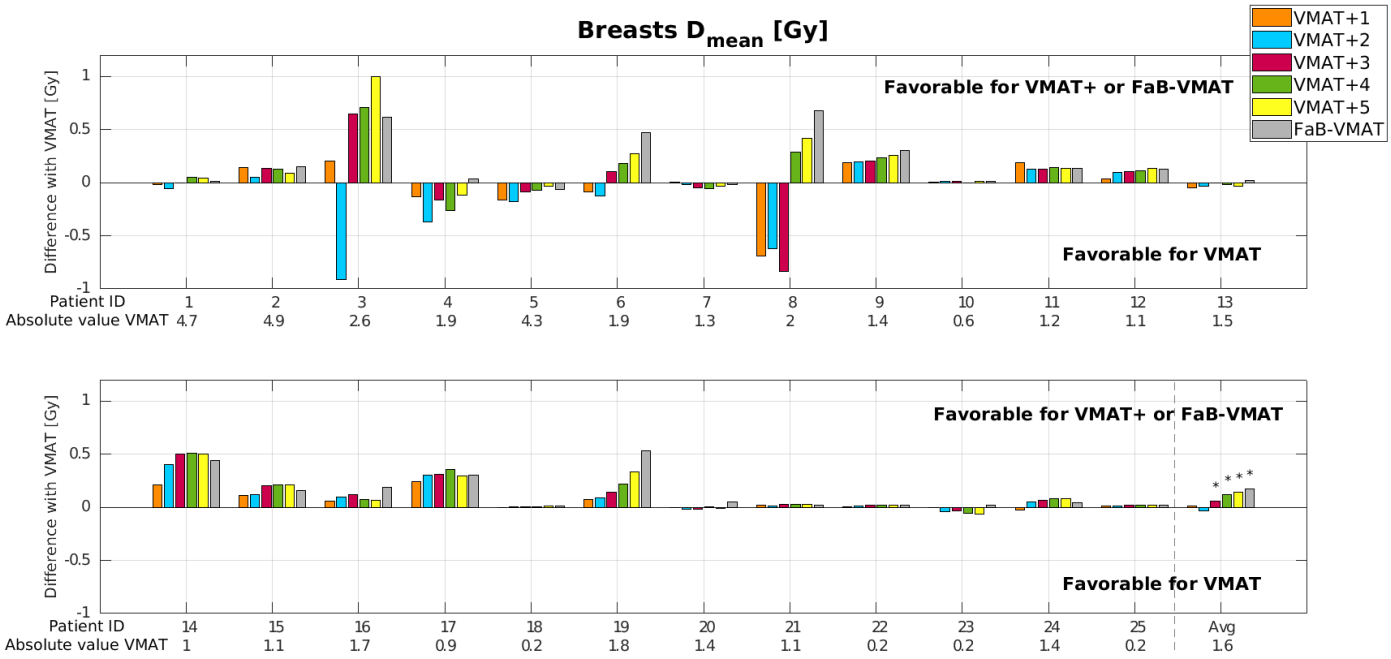
- **Breasts**: Breasts are the organ that got on average affected the least by differences in beam configuration. Doses went from minimum of 1.7 Gy and 9.4% with VMAT to 1.5 Gy and to 8.0% with FaB-VMAT, for D_{mean} and $V_{4\,Gy}$, respectively). For most patients, differences between plans were considered not clinically significant, but they were sometimes (very) large for some, as visible in figure 4.4a and 4.4b.

- **Heart**: On average, VMAT+2, VMAT+3, VMAT+4 and VMAT+5 plans were equally the best as visible in figure 4.4c. FaB-VMAT heart D_{mean} was, on average, higher than VMAT+ and lower than VMAT. The differences were clinically relevant only for some patients as visible in figure 4.4c.

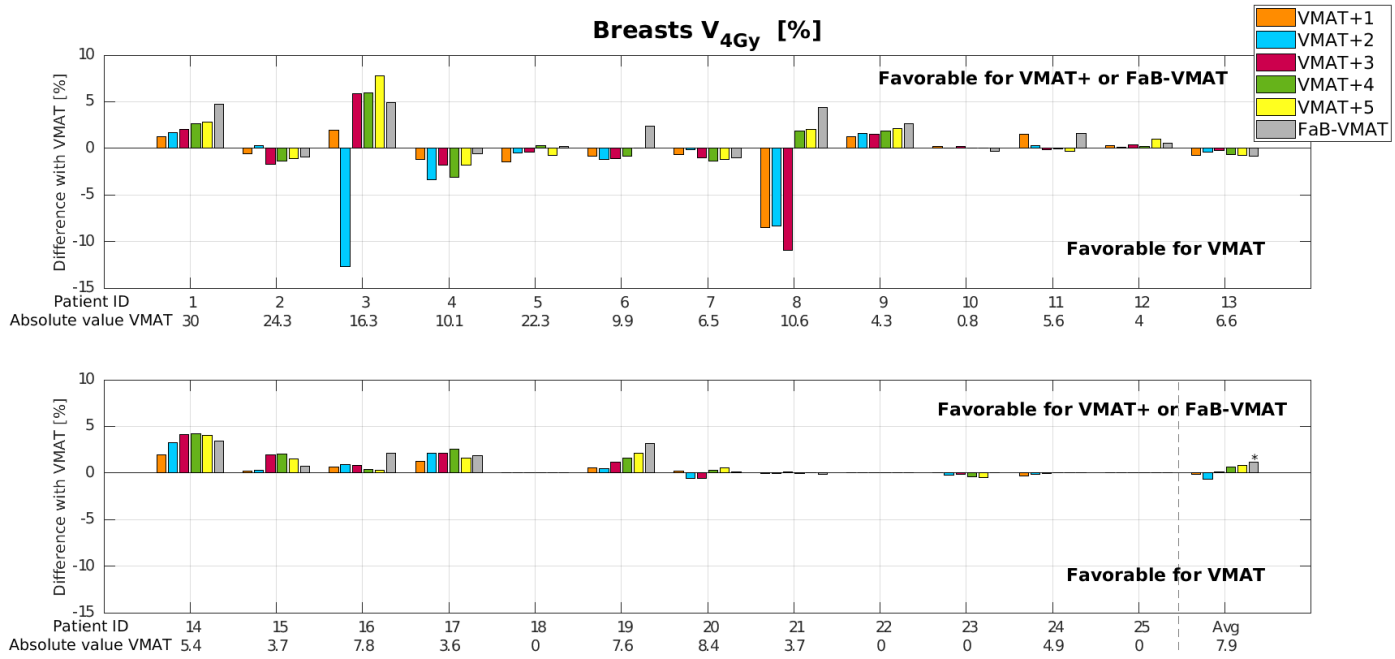
- **Lungs**: VMAT+5 was on average best for D_{mean}, and $V_{5\,Gy}$ and $V_{20\,Gy}$, with statistically significant differences with VMAT, FaB-VMAT and all other VMAT+ plans (figure E.1h to E.1j). Clinical significance depended on patients as visible in figure 4.4d. For VMAT+ plans, there is a trend of increasingly lower lungs doses with added number of plus beams, with improvements between consecutive plans generally statistically significant (see figure 4.4d to 4.4f and figure E.1h to E.1j).

- **Patient Doses**: Adding beams on average improved patient doses ($V_{5\,Gy}$ and $V_{20\,Gy}$), with VMAT+5 the best. Differences were not always statistically and clinically relevant, but for some patients a clear and relevant improvement can be achieved with for instance VMAT+5 compared to VMAT or VMAT+1, as in patient 7 in figure 4.3.

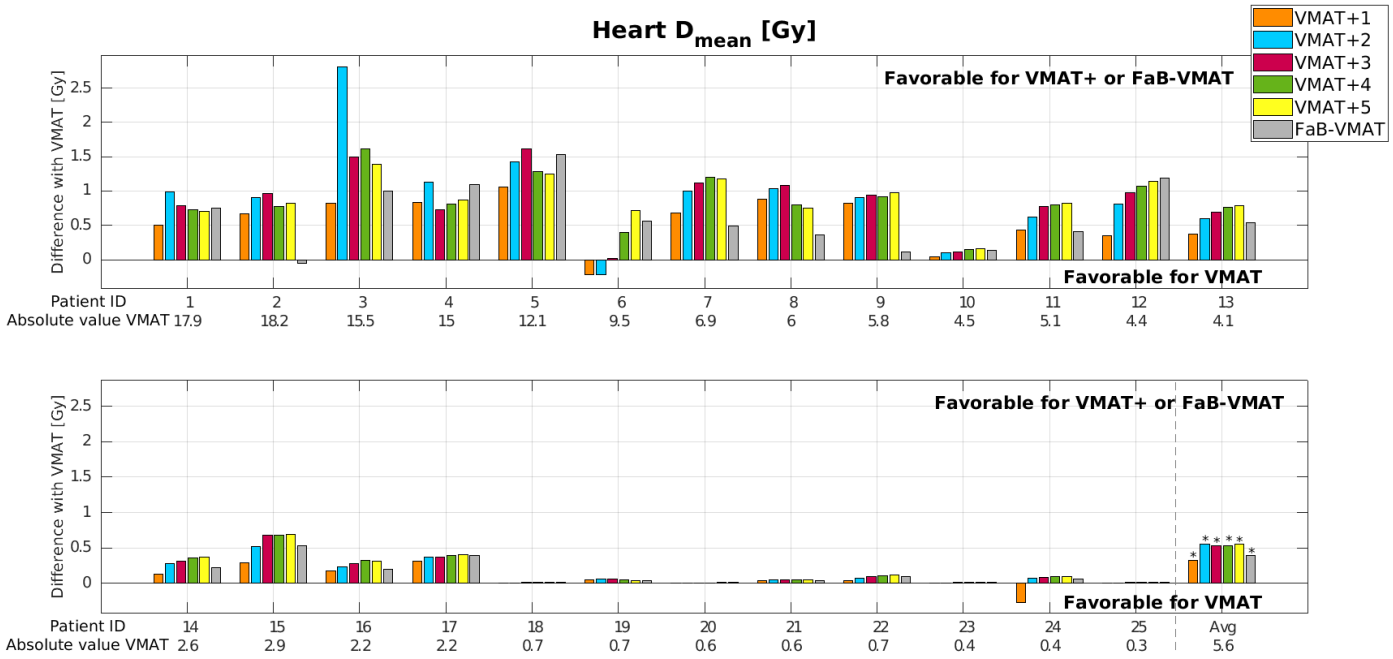
- **Conformity index**: VMAT+5 plans were best (CI closer to 1) and VMAT was the worst (figure 4.4i). Added number of beams, on average, improved conformality (figure E.1d).


Breasts D mean [Gy]
VMAT+1
VMAT+2
VMAT+3
VMAT+4
VMAT+5
FaB-VMAT
Favorable for VMAT+ or FaB-VMAT
Favorable for VMAT
Difference with VMAT [Gy]
Patient ID
Absolute value VMAT
1 2 3 4 5 6 7 8 9 10 11 12 13
4.7 4.9 2.6 1.9 4.3 1.9 1.3 2 1.4 0.6 1.2 1.1 1.5
14 15 16 17 18 19 20 21 22 23 24 25 Avg
1 1.1 1.7 0.9 0.2 1.8 1.4 1.1 0.2 0.2 1.4 0.2 1.6

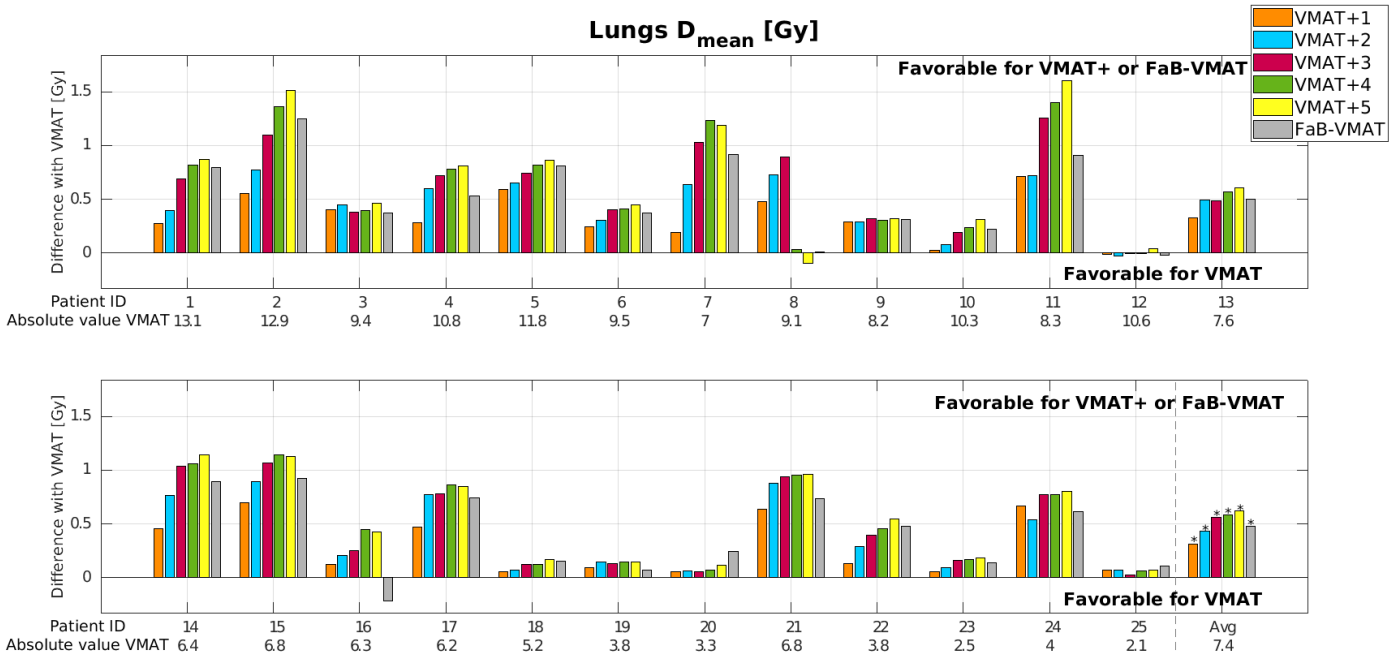
(a)


Breasts V 4Gy [%]
VMAT+1
VMAT+2
VMAT+3
VMAT+4
VMAT+5
FaB-VMAT
Favorable for VMAT+ or FaB-VMAT
Favorable for VMAT
Difference with VMAT [%]
Patient ID
Absolute value VMAT
1 2 3 4 5 6 7 8 9 10 11 12 13
30 24.3 16.3 10.1 22.3 9.9 6.5 10.6 4.3 0.8 5.6 4 6.6
14 15 16 17 18 19 20 21 22 23 24 25 Avg
5.4 3.7 7.8 3.6 0 7.6 8.4 3.7 0 0 4.9 0 7.9

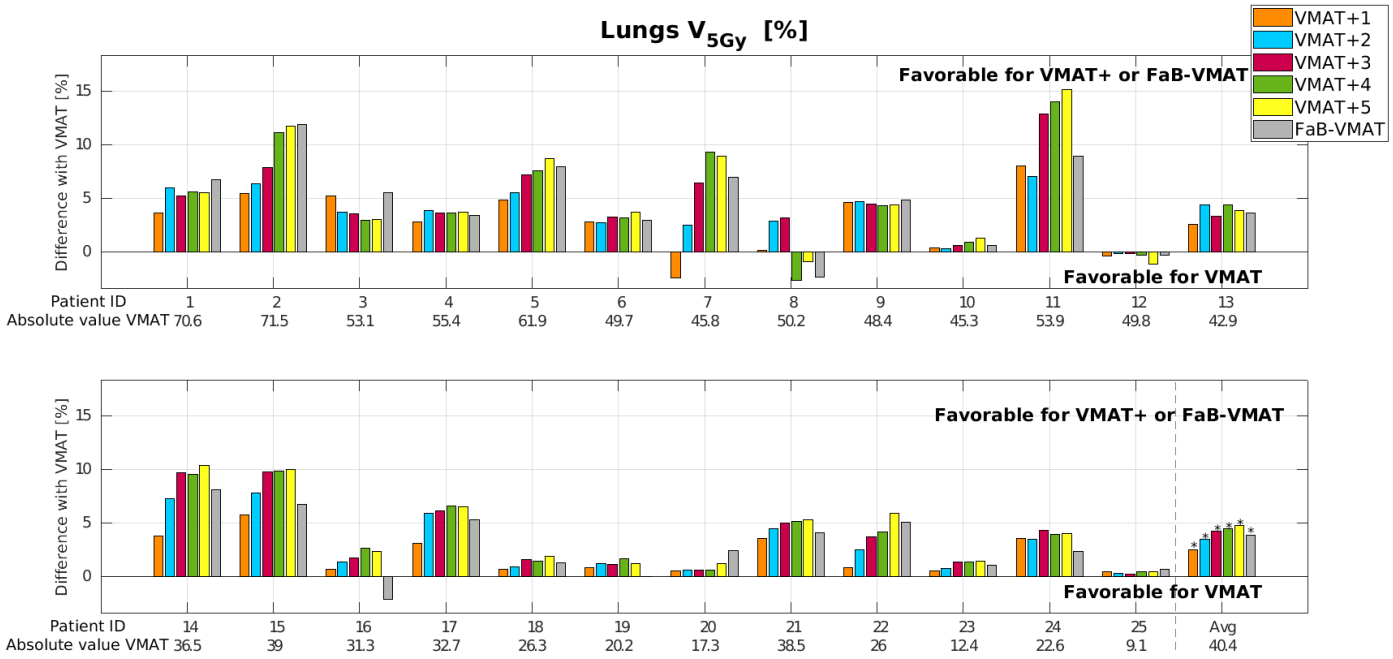
(b)


Heart D mean [Gy]
VMAT+1
VMAT+2
VMAT+3
VMAT+4
VMAT+5
FaB-VMAT
Favorable for VMAT+ or FaB-VMAT
Favorable for VMAT
Difference with VMAT [Gy]
Patient ID 1 2 3 4 5 6 7 8 9 10 11 12 13
Absolute value VMAT 17.9 18.2 15.5 15 12.1 9.5 6.9 6 5.8 4.5 5.1 4.4 4.1
Favorable for VMAT+ or FaB-VMAT
Favorable for VMAT
Difference with VMAT [Gy]
Patient ID 14 15 16 17 18 19 20 21 22 23 24 25 Avg
Absolute value VMAT 2.6 2.9 2.2 2.2 0.7 0.7 0.6 0.6 0.7 0.4 0.4 0.3 5.6

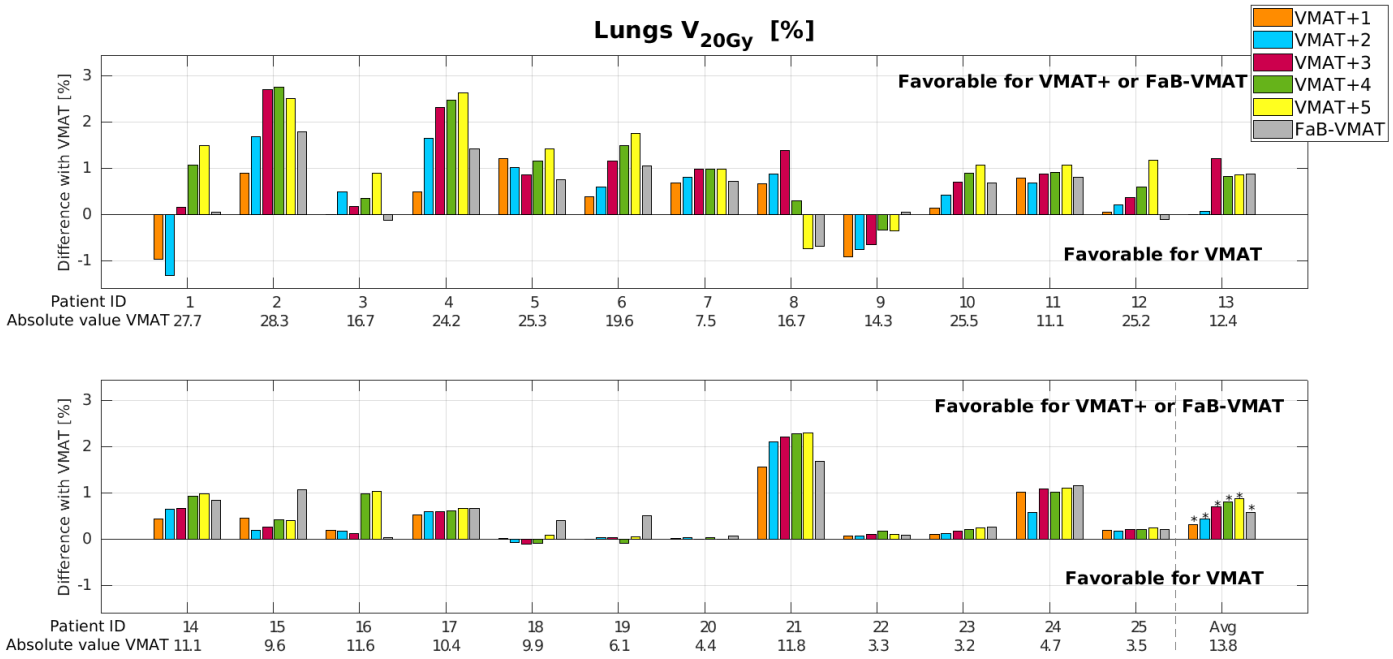
(c)


Lungs D mean [Gy]
VMAT+1
VMAT+2
VMAT+3
VMAT+4
VMAT+5
FaB-VMAT
Favorable for VMAT+ or FaB-VMAT
Favorable for VMAT
Difference with VMAT [Gy]
Patient ID 1 2 3 4 5 6 7 8 9 10 11 12 13
Absolute value VMAT 13.1 12.9 9.4 10.8 11.8 9.5 7 9.1 8.2 10.3 8.3 10.6 7.6
Favorable for VMAT+ or FaB-VMAT
Favorable for VMAT
Difference with VMAT [Gy]
Patient ID 14 15 16 17 18 19 20 21 22 23 24 25 Avg
Absolute value VMAT 6.4 6.8 6.3 6.2 5.2 3.8 3.3 6.8 3.8 2.5 4 2.1 7.4

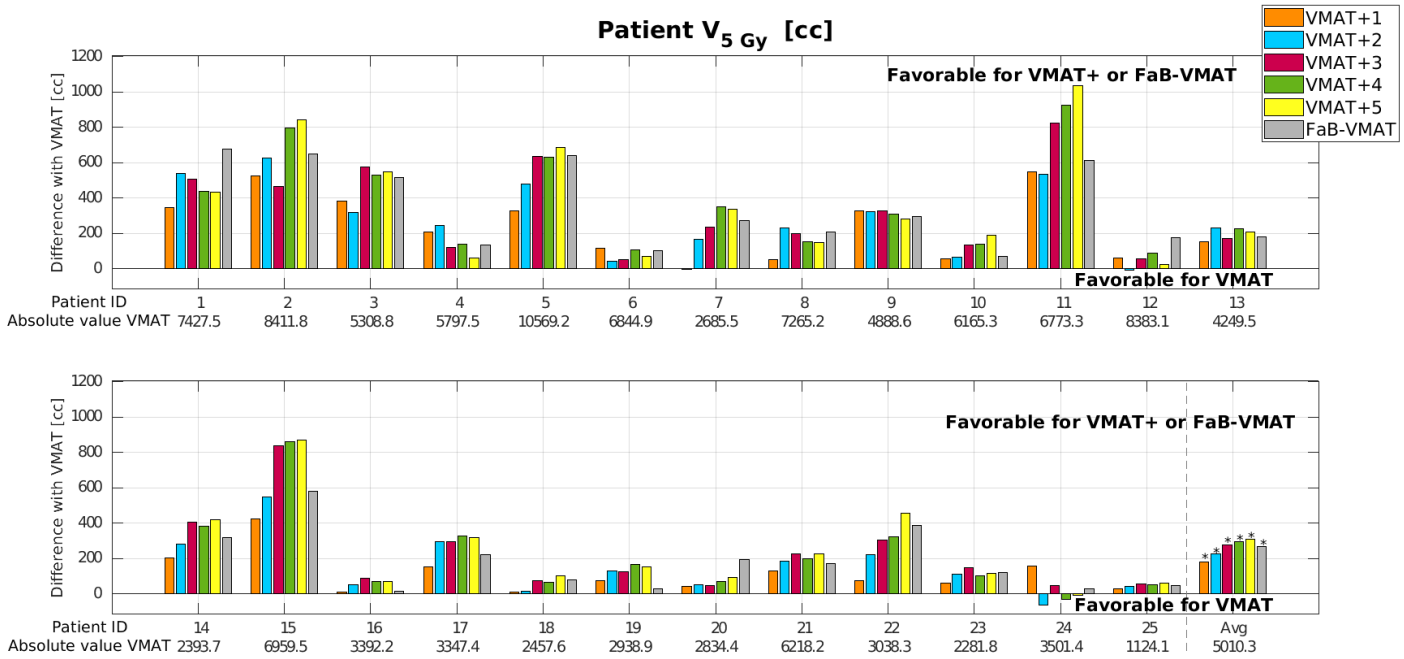
(d)


Lungs V5Gy [%]
VMAT+1
VMAT+2
VMAT+3
VMAT+4
VMAT+5
FaB-VMAT
Favorable for VMAT+ or FaB-VMAT
Favorable for VMAT
Difference with VMAT [%]
Patient ID 1 2 3 4 5 6 7 8 9 10 11 12 13
Absolute value VMAT 70.6 71.5 53.1 55.4 61.9 49.7 45.8 50.2 48.4 45.3 53.9 49.8 42.9
Patient ID 14 15 16 17 18 19 20 21 22 23 24 25 Avg
Absolute value VMAT 36.5 39 31.3 32.7 26.3 20.2 17.3 38.5 26 12.4 22.6 9.1 40.4

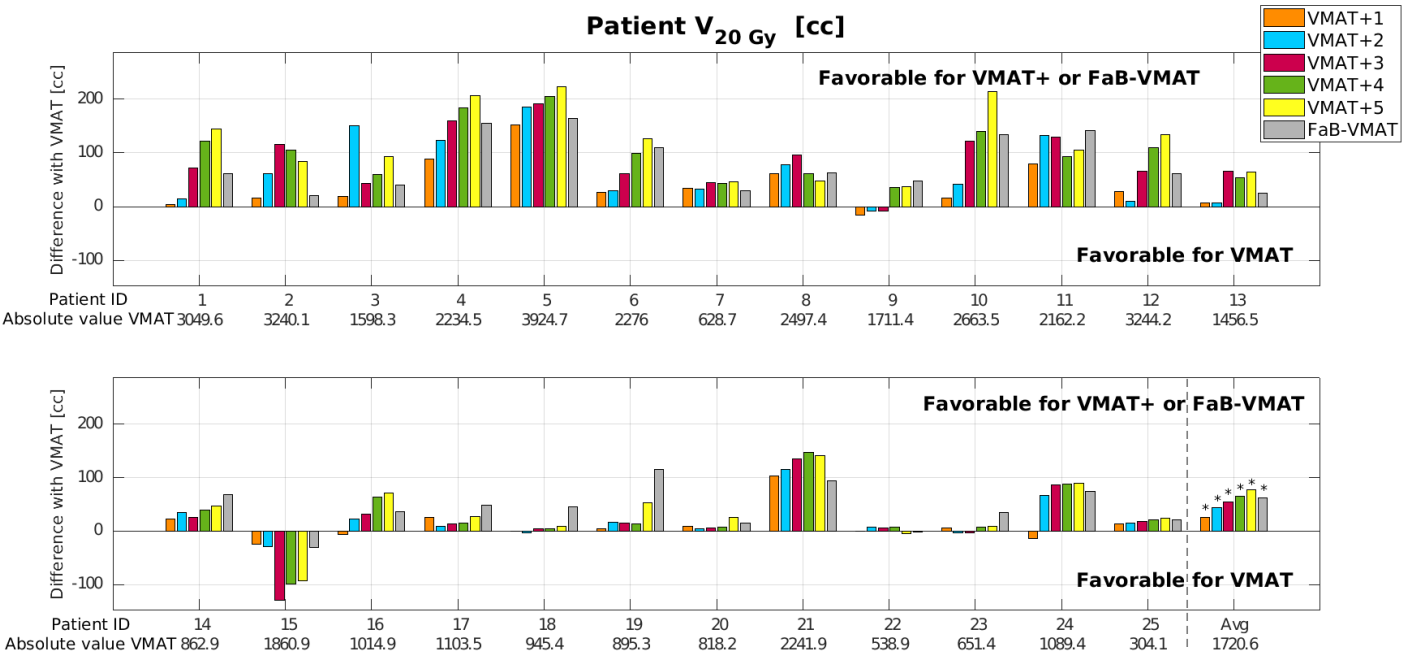
(e)


Lungs V20Gy [%]
VMAT+1
VMAT+2
VMAT+3
VMAT+4
VMAT+5
FaB-VMAT
Favorable for VMAT+ or FaB-VMAT
Favorable for VMAT
Difference with VMAT [%]
Patient ID 1 2 3 4 5 6 7 8 9 10 11 12 13
Absolute value VMAT 27.7 28.3 16.7 24.2 25.3 19.6 7.5 16.7 14.3 25.5 11.1 25.2 12.4
Patient ID 14 15 16 17 18 19 20 21 22 23 24 25 Avg
Absolute value VMAT 11.1 9.6 11.6 10.4 9.9 6.1 4.4 11.8 3.3 3.2 4.7 3.5 13.8

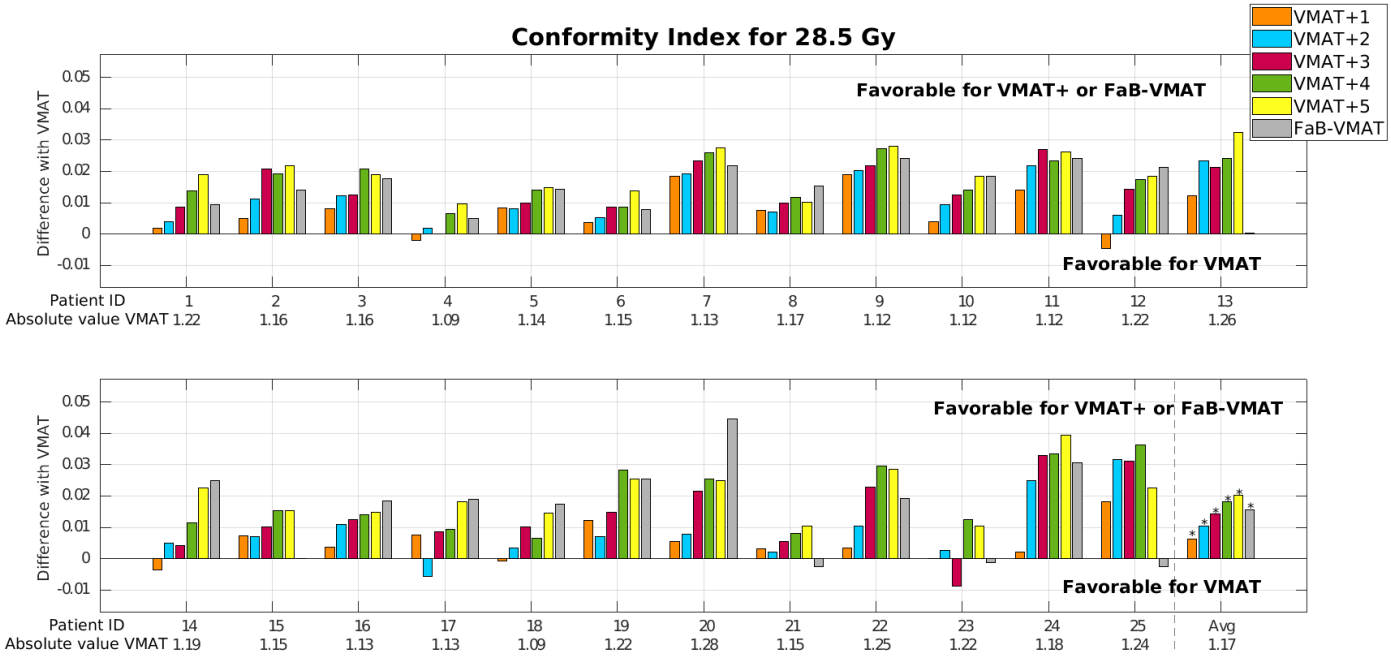
(f)


Patient V5 Gy [cc]
VMAT+1
VMAT+2
VMAT+3
VMAT+4
VMAT+5
FaB-VMAT
Favorable for VMAT+ or FaB-VMAT
Favorable for VMAT
Difference with VMAT [cc]
Patient ID
Absolute value VMAT
1 2 3 4 5 6 7 8 9 10 11 12 13
7427.5 8411.8 5308.8 5797.5 10569.2 6844.9 2685.5 7265.2 4888.6 6165.3 6773.3 8383.1 4249.5
14 15 16 17 18 19 20 21 22 23 24 25 Avg
2393.7 6959.5 3392.2 3347.4 2457.6 2938.9 2834.4 6218.2 3038.3 2281.8 3501.4 1124.1 5010.3

(g)


Patient V20 Gy [cc]
VMAT+1
VMAT+2
VMAT+3
VMAT+4
VMAT+5
FaB-VMAT
Favorable for VMAT+ or FaB-VMAT
Favorable for VMAT
Difference with VMAT [cc]
Patient ID
Absolute value VMAT
1 2 3 4 5 6 7 8 9 10 11 12 13
3049.6 3240.1 1598.3 2234.5 3924.7 2276 628.7 2497.4 1711.4 2663.5 2162.2 3244.2 1456.5
14 15 16 17 18 19 20 21 22 23 24 25 Avg
862.9 1860.9 1014.9 1103.5 945.4 895.3 818.2 2241.9 538.9 651.4 1089.4 304.1 1720.6

(h)



(i)

Figure 4.4: Comparisons of VMAT+ plan parameters with VMAT for a) breasts D_{mean} and b) $V_{4\,Gy}$, c) heart D_{mean}, d) lungs D_{mean}, e) $V_{5\,Gy}$ and f) $V_{20\,Gy}$, g) patient $V_{5\,Gy}$ and h) $V_{20\,Gy}$ and i) PTV CI for 28.5% (95% of prescribed dose). VMAT values for each parameter are reported below the patient ID. * points at statistically significant differences with VMAT. Positive is favorable for VMAT+ and FaB-VMAT; Negative is favorable for VMAT. Patients were ordered according to descending heart D_{mean}.

4.2.2.4 Analysis for a selected patient

In this section VMAT, VMAT+3, VMAT+5 and FaB-VMAT are analyzed, in some detail for one patient.

Patient 11

Patient 11 has a large bilateral tumor, from the mandible and neck to the center of the mediastinum, see figure 4.1.

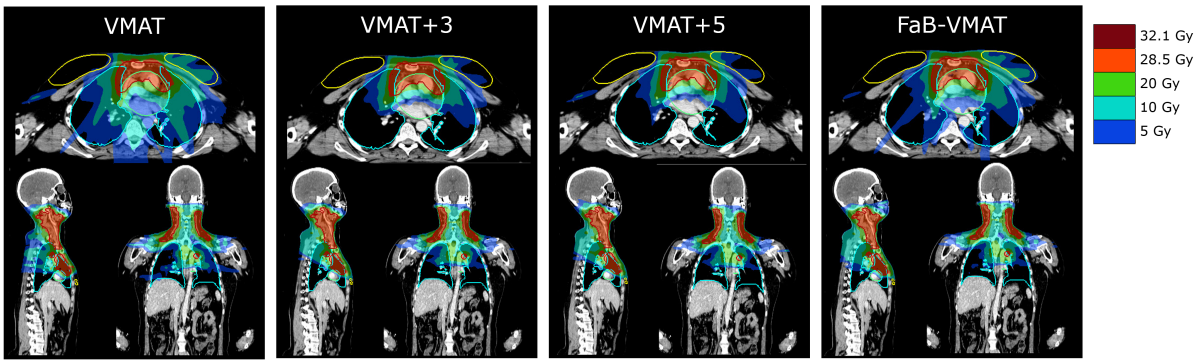


Figure 4.5: Dose distributions for patient 11. PTV delineated in red, breasts delineated in yellow, lungs in blue and heart in green.

In figure 4.5 differences between dose distributions for the different techniques are clearly visible. VMAT+5 resulted in a much more conformal dose distribution, both at low and higher doses.

VMAT+3, VMAT+4 and VMAT+5 plans performed similarly for OAR sparing, and better than VMAT for all parameters except breasts $V_{4\,Gy}$, and better than FaB-VMAT for heart D_{mean}, and lungs D_{mean} and $V_{5\,Gy}$. Moreover, VMAT+5 reduced heart and lungs D_{mean} by 0.9 Gy and 1.7 Gy, compared to VMAT, respectively.

All parameters (apart from breasts doses) decrease with added number of beams, from VMAT to VMAT+3 to VMAT+5.

4.2.3 Subjective plan selection by observers

Results of subjective plan selections by reviewers are presented in figure 4.6: based on plan quality in figure 4.6a, and based on plan quality and delivery time in figure 4.6b. The figure clearly shows a large variation in plan selection among observers and the variation can be highly patient-specific.

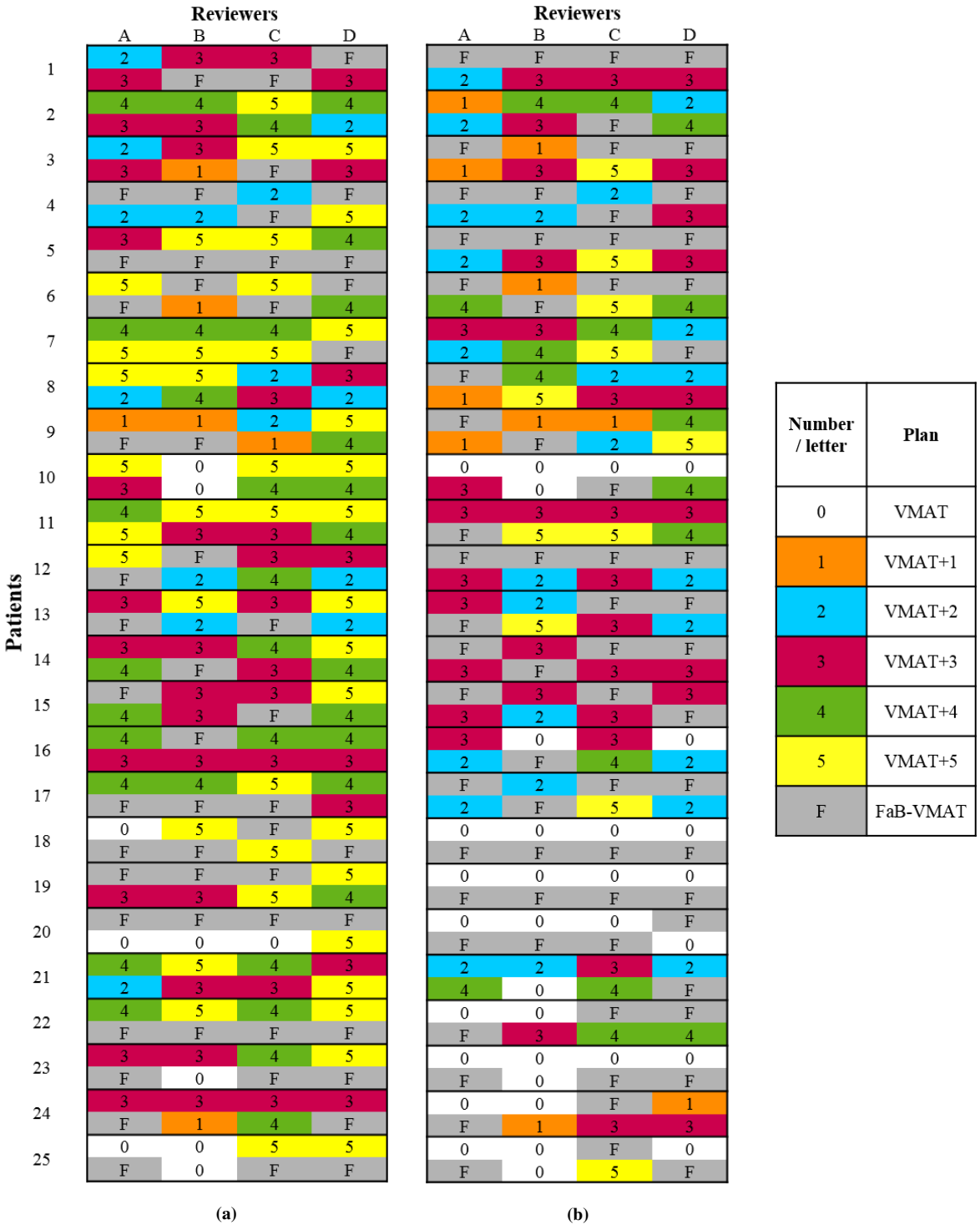
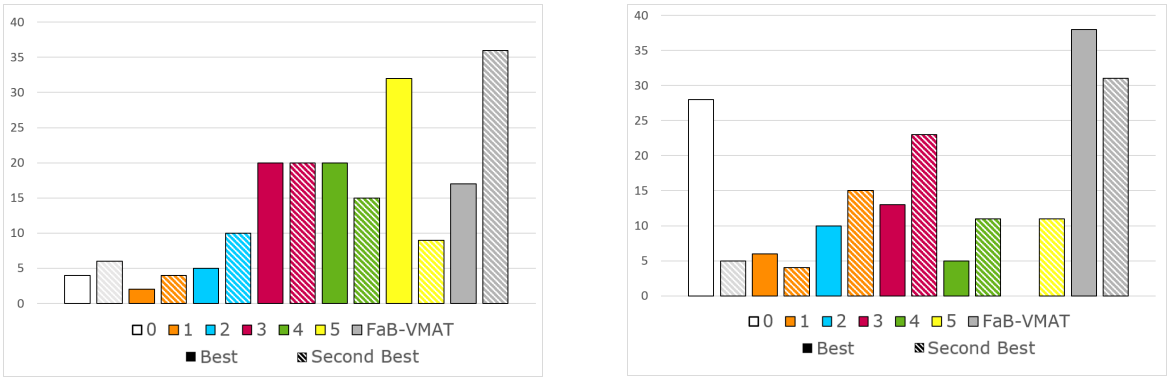


Figure 4.6: Plans chosen by each reviewer based on a) perceived plan quality and b) plan quality and delivery time. Each reviewer chose the best and second best plan for each patient, i.e. for patient 1, reviewer A chose as best plan VMAT+2 and as second best VMAT+3 if only plan quality was considered.

When performing plan selection based on plan quality only, VMAT+5 was the plan selected the most as first option and FaB-VMAT was selected the most as second option as visible in figure 4.7a. VMAT, VMAT+1 and VMAT+2 were barely selected either as best or second best.

When considering also delivery time for plan selection, FaB-VMAT was the most selected plan, both as the best and second best option (see figure 4.7b). As alternative, VMAT was the most selected as first option and VMAT+3 as second option (see figure 4.7a and 4.7b).



(a) (b)

Figure 4.7: Frequency with which plans were selected as best and second option when considering a) plan quality and b) plan quality and delivery time. Solid bars report plans selected as best; dashed bars report plans selected as second best.

Comparing the plans selected in each selection, there is a significant increase in selection of VMAT and FaB-VMAT when delivery time is considered (figure 4.8). VMAT+ with more than 3 beams were selected more when delivery time was not considered.

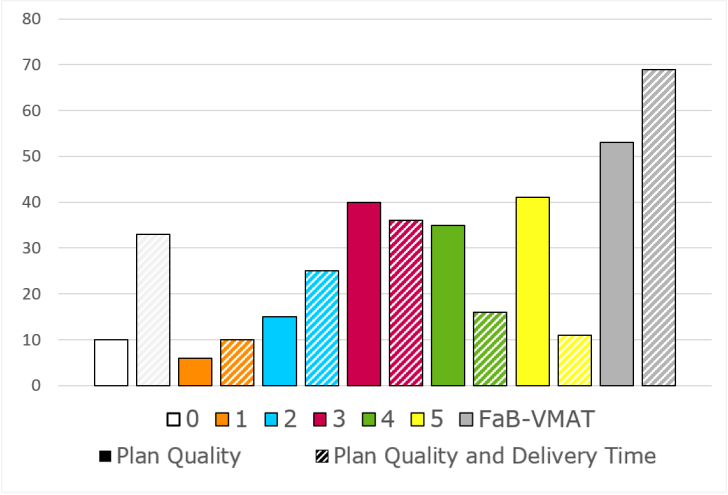


Figure 4.8: Frequency with which plans were selected either as best and second best plan. Solid bars report plan selection based on only plan quality; dashed bars report plan selection based on plan quality and delivery time

Figure 4.9 represents the frequency with which each plan was selected as the best one by at least 3 observes, considering plan quality and plan quality and delivery time. FaB-VMAT was clearly the most unanimously selected plan, considering or not delivery time. VMAT was unanimously considered best plan only when delivery time was also considered. There was never consensus on selecting VMAT+5 when time was considered.

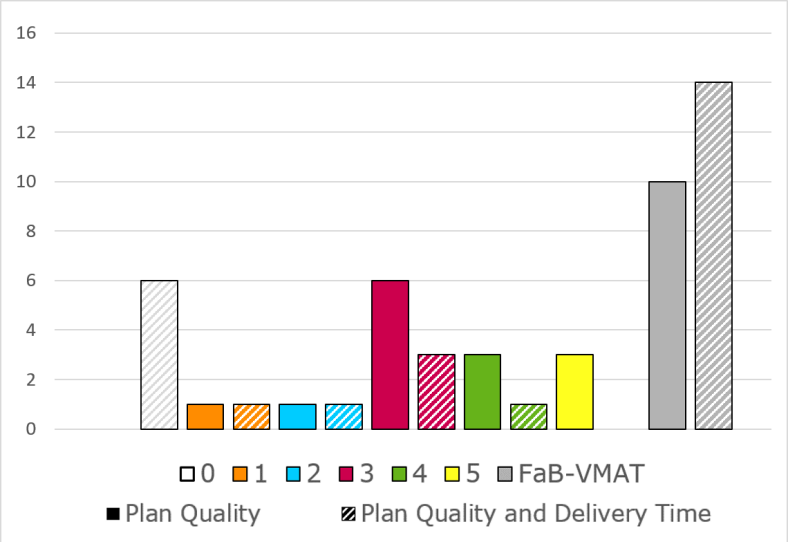


Figure 4.9: Frequency of plan selected as either first or second option, unanimously by at least 3 reviewers. Solid bars report plan selection based on only plan quality; dashed bars report plan selection based on plan quality and delivery time.

4.2.4 Weight of non-coplanar beams in VMAT+5 plans

For VMAT+5 plans, most of the weight for PTV Dmean comes from VMAT contribution (see figure 4.10), but contributions of the non-coplanar beams are substantial, depending on the patient. The contribution of the 5 VMAT+ beams was on average 35.7%, but with a minimum of 19.4% and a maximum of 53.0% weight among all patients.

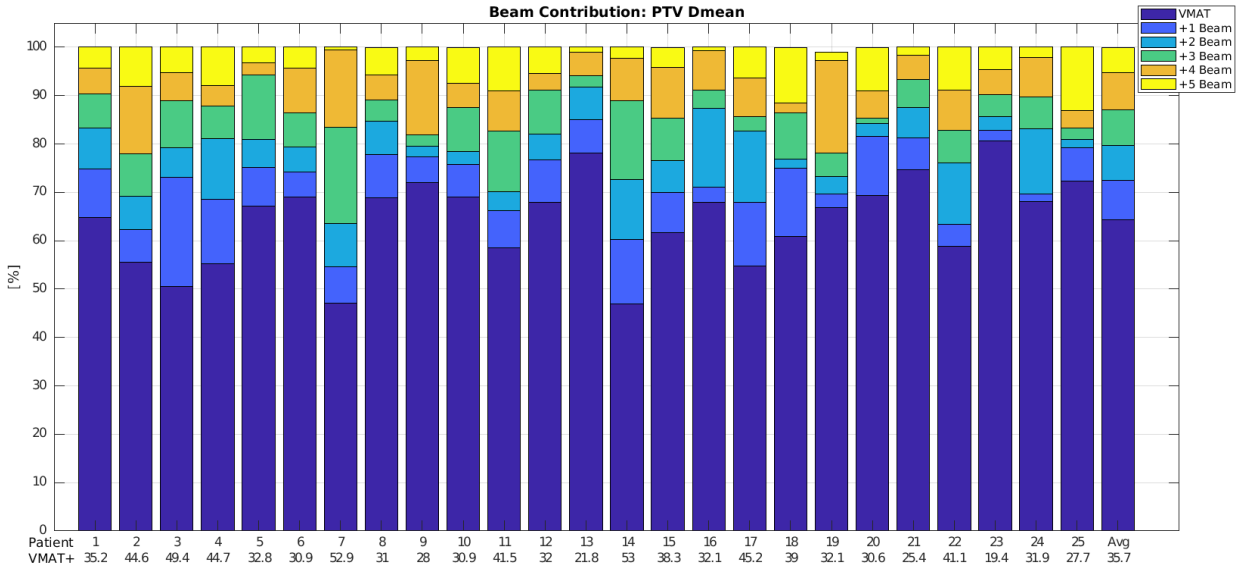


Figure 4.10: Contribution for PTV D_{mean} from VMAT (dark blue) and added plus beams (+1 to +5). For each patient, VMAT+ total contribution is stated below patient number.

4.3 Discussion

In this study, we have used automated plan generation to investigate the added value of different non-coplanar beam configurations for mediastinal lymphoma patients. In line with the conclusions from Rossi and Cambraia Lopes, et al. [11], non-coplanar beam configurations were superior to coplanar beam configurations.

VMAT+ plan quality increases, on average, with added number of beams: reduced D_{mean} in heart and lungs; reduced lungs and patient $V_{5\,Gy}$ and $V_{20\,Gy}$, and higher conformality. Which suggests that an increased level of non-coplanarity increases sparing, as in [11], even if the clinical relevance of these differences can vary among patients.

FaB-VMAT had reduced low-dose spread in breasts and patient compared to VMAT+ plans with few added beams (< 3). The FaB-VMAT configuration aimed to reduce dose to the heart. Levis et al. [10] reported that FaB-VMAT resulted in higher sparing for heart D_{mean} and breasts D_{mean}, with increases in breasts $V_{4\,Gy}$. For the patients in this study, heart D_{mean} was usually lower for VMAT+3, VMAT+4 or VMAT+5 but FaB-VMAT performed better in the breasts. Conformality was also better for VMAT+5.

Mediastinal lymphoma patients have very diverse anatomical presentations, which hinders finding a beam configuration suitable for many patients. VMAT+4, VMAT+5 and FaB-VMAT were overall the best for the patient population, but many of the differences between plans were small and no configuration was unanimously the best for all OARs for some OAR there was no consistent highest-sparing plan for all organs. As for this treatment site in particular there is not a clear order of priority for OAR sparing, choosing one plan over the others was not trivial.

Non-coplanar plans are more time consuming than coplanar plans. With an added number of non-coplanar beams, as opposed to non-coplanar and partial arcs, delivery time increases even more. Faster treatments are easier to deliver, more comfortable for the patient and there is less chance of motion-induced dose errors, so delivery time may often be decisive when choosing a plan, which favors FaB-VMAT. However, faster solutions as VMAT or FaB-VMAT may not be optimal for all patients. VMAT+ plans sometimes allow higher specificity which for some patient may be beneficial, justifying the longer treatment times. This is also reflected in the analysis on plan selection by reviewers, showing that slower VMAT+ plans were selected in a substantial number of cases, also if treatment delivery time was taking into account in decision making.

When plan selection was performed by 4 reviewers, it was clearly influenced by delivery time. FaB-VMAT was the most selected plan, considering plan quality and delivery time. For most patients, VMAT+ plans have a higher plan quality than VMAT, but increase in delivery time was not always found justifiable.

FaB-VMAT plans were considered high-quality plans, with a positive dose distribution quality-delivery time balance. Even so, for several patients, VMAT+ plans were still justified, which reflects the need for a wider range of plans for each patient than just VMAT and FaB-VMAT.

The 5 patient-optimized beams in VMAT+5 were relevant to PTV D_{mean} contribution, with the weight of the 5^{th} beam being, on average, the lowest.

4.4 Conclusions

For 25 mediastinal lymphoma patients, VMAT, FaB-VMAT and VMAT+ plans were automatically generated and compared. Non-coplanar configurations were superior to conventional coplanar VMAT. VMAT+ resulted in reduced heart and lungs mean doses, and lungs and patient $V_{5\,Gy}$ and $V_{20\,Gy}$, and higher conformity, for most patients, compared to VMAT, but gain was patient-specific. FaB-VMAT presents consistently high-quality plans, similar to VMAT+4 and VMAT+5, with limited optimization and delivery time. Several patients may benefit from patient-specific VMAT+ plans over FaB-VMAT, justifying the increased treatment time. Thanks to automated planning, VMAT, VMAT+ and FaB-VMAT could be generated and compared for each patient to select the optimal dose distribution for each patient.

5 Final discussion and conclusions about VMAT+ for nasopharyngeal carcinoma and mediastinal lymphoma

Plan quality improved when adding patient-optimized non-coplanar IMRT beams to coplanar VMAT, for both nasopharyngeal carcinoma and mediastinal lymphoma. VMAT+ with more than 2 added beams tended to be most beneficial, but VMAT+4 and VMAT+5 were considered too time-consuming for many patients.

For nasopharyngeal carcinoma, VMAT+3 was found to be the most appropriate treatment, with a positive dose distribution quality-delivery time balance. For mediastinal lymphoma, VMAT+5 provides high-quality plans. However, FaB-VMAT provided similar plan quality as most VMAT+ plans, with lower delivery time. VMAT+5 would be the most selected first option when considering only plan quality, but FaB-VMAT is often the best choice when both plan quality and delivery time are considered.

Previous research into the VMAT+ technique applied it to liver and prostate stereotactic body radiation therapy (SBRT) [41, 42]. For liver, plan quality was enhanced compared to VMAT by adding 1-5 patient-optimized non-coplanar IMRT beams. For prostate, the generated VMAT+ plans lead to a class solution with the two most preferred directions, which increased plan quality compared to VMAT, for all patients, with limited increase in treatment time.

Both of the already studied treatment sites used SBRT, which involves higher doses of radiation per treatment fraction than in the conventional delivery scheme, used for NPC and ML. Even though NPC and ML are both treatment sites where tumors tend to have larger sizes, it was hypothesized that VMAT+ would be beneficial because NPC is a complex, multiple structures treatment site and ML showed benefits for non-coplanar configurations (as in [11]). VMAT+ was indeed beneficial for both treatment sites, surpassing the plan quality of coplanar VMAT plans. VMAT+ may be a very useful technique for localized tumors, such as other head and neck, lungs and pancreatic cancer.

Patient-specific VMAT+ generation was only possible because of our in-house optimizer for fully automated, multi-criteria beam angle selection and IMRT beam profile optimization. The overall benefit of VMAT+ plans is indicative of the need for non-coplanar approaches.

For both NPC and ML, the best treatment approach may depend on the specific patient anatomy. With automated planning, more plans could be generated per patient, allowing to select the best-individualized treatment approach for each patient.

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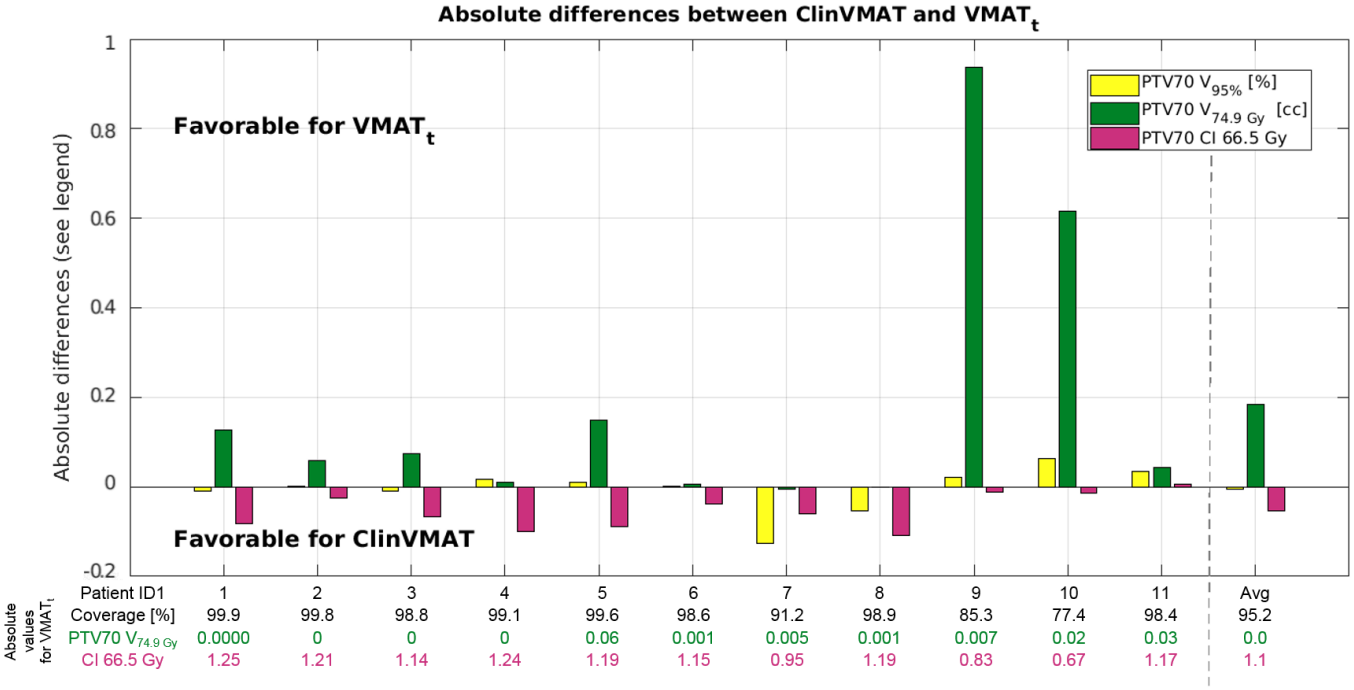
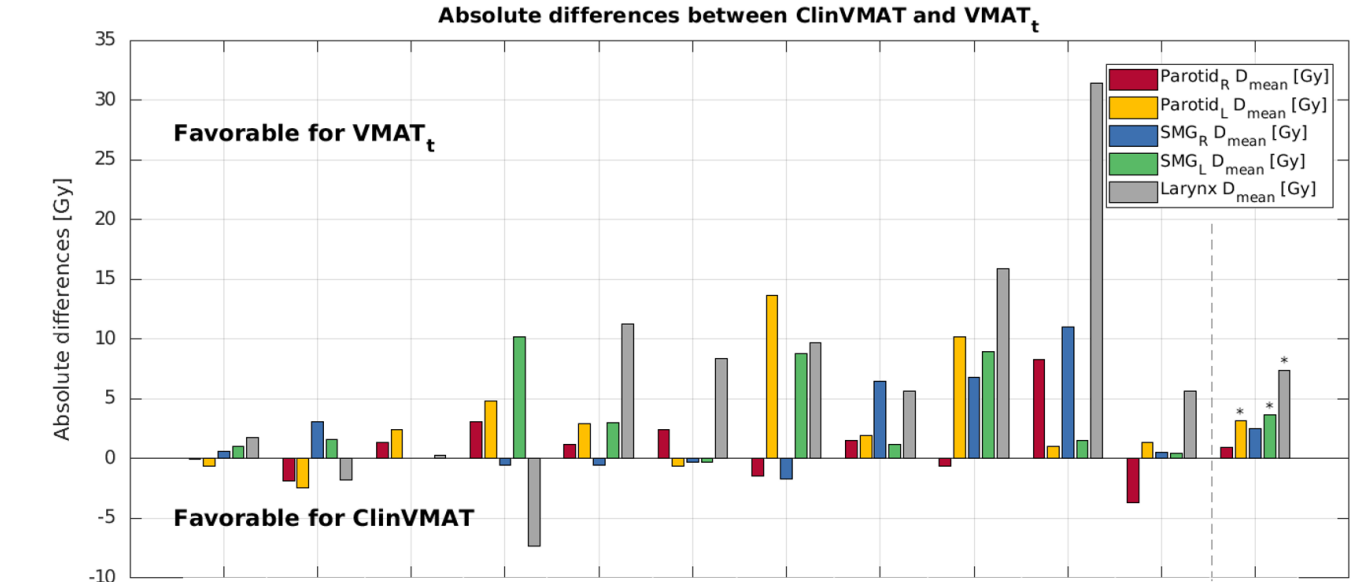
A Differences between manually and automatically generated VMAT for all nasopharyngeal carcinoma patients



Absolute values for VMAT$_t$

Patient ID1	1	2	3	4	5	6	7	8	9	10	11	Avg
Coverage [%]	99.9	99.8	98.8	99.1	99.6	98.6	91.2	98.9	85.3	77.4	98.4	95.2
PTV70 $V_{74.9\ Gy}$	0.0000	0	0	0	0.06	0.001	0.005	0.001	0.007	0.02	0.03	0.0
CI 66.5 Gy	1.25	1.21	1.14	1.24	1.19	1.15	0.95	1.19	0.83	0.67	1.17	1.1

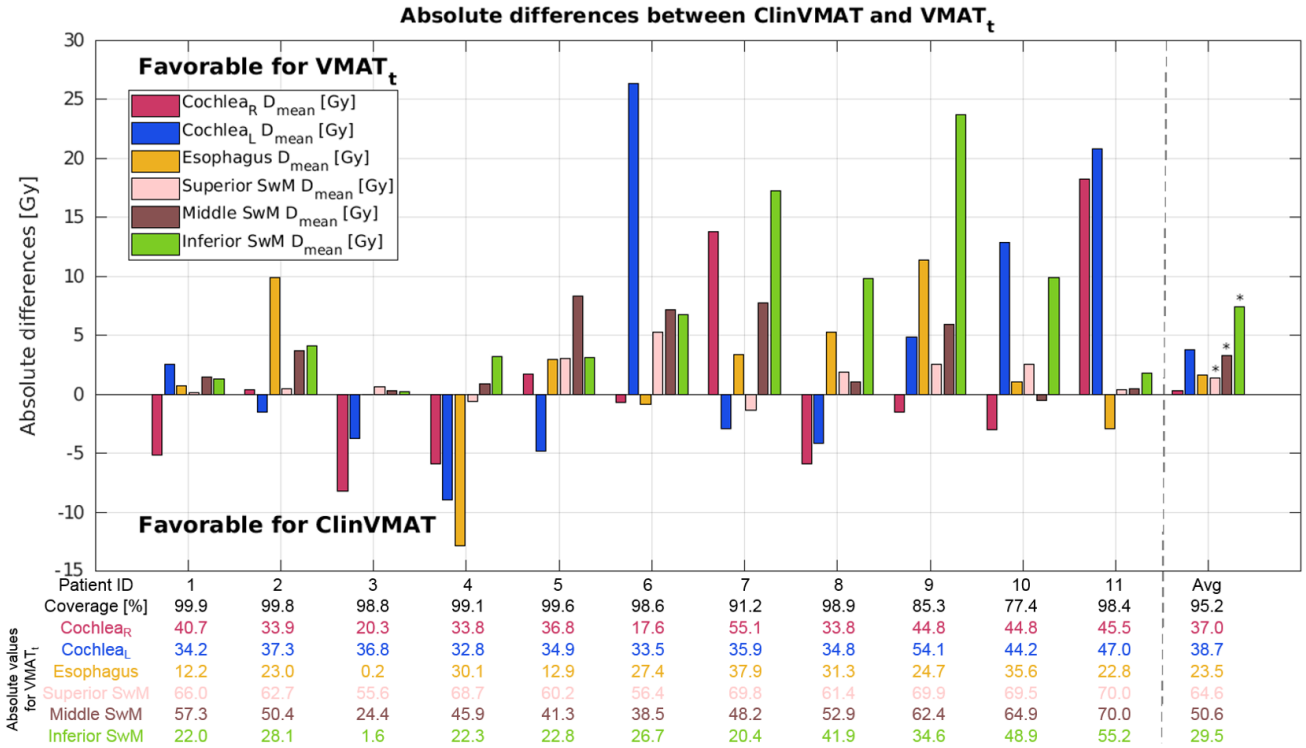
(a)



Absolute values for VMAT$_t$

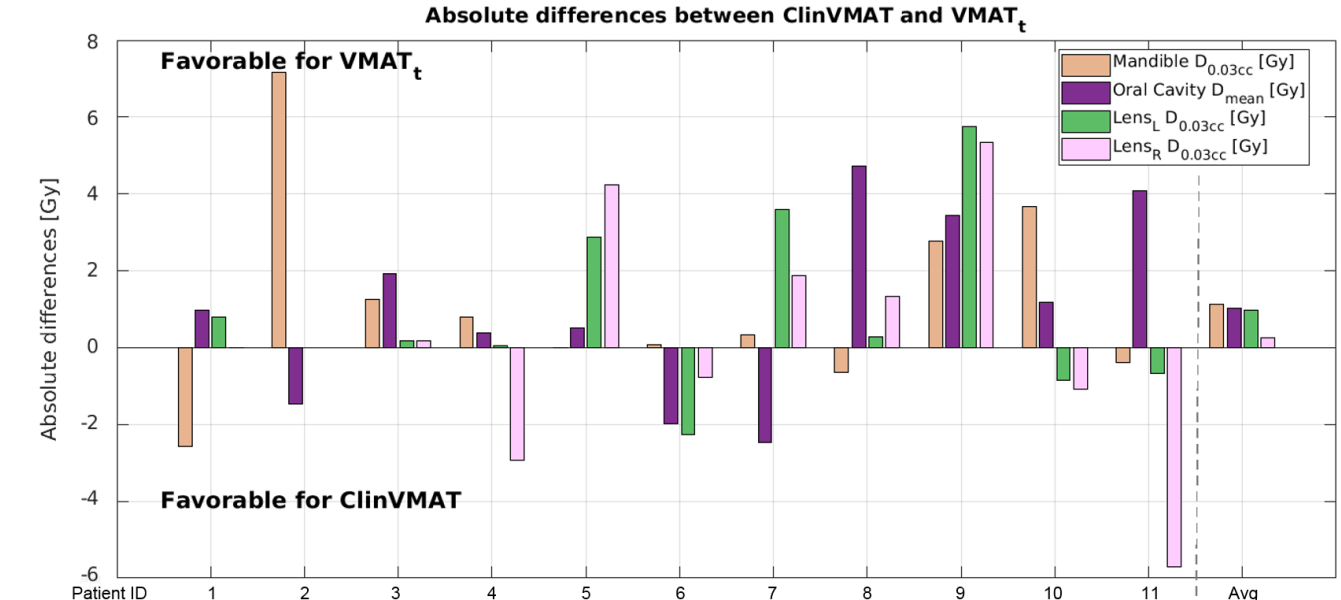
Patient ID1	1	2	3	4	5	6	7	8	9	10	11	Avg
Coverage [%]	99.9	99.8	98.8	99.1	99.6	98.6	91.2	98.9	85.3	77.4	98.4	95.2
Parotid$_R$	20.7	28.7	7.8	30.4	32.5	22.7	64.8	22.0	62.4	46.1	50.1	35.3
Parotid$_L$	25.1	28.4	44.7	40.5	24.6	41.9	33.9	30.9	49.4	66.3	59.5	40.5
SMG$_R$	39.9	34.6	ND	68.1	70.6	34.8	69.9	44.5	59.4	51.1	68.2	54.1
SMG$_L$	36.0	39.1	ND	49.6	35.9	70.0	34.1	64.0	51.6	67.2	67.7	51.5
Larynx	31.6	36.1	11.3	33.2	33.4	33.9	27.0	35.2	39.6	17.1	43.1	31.0

(b)



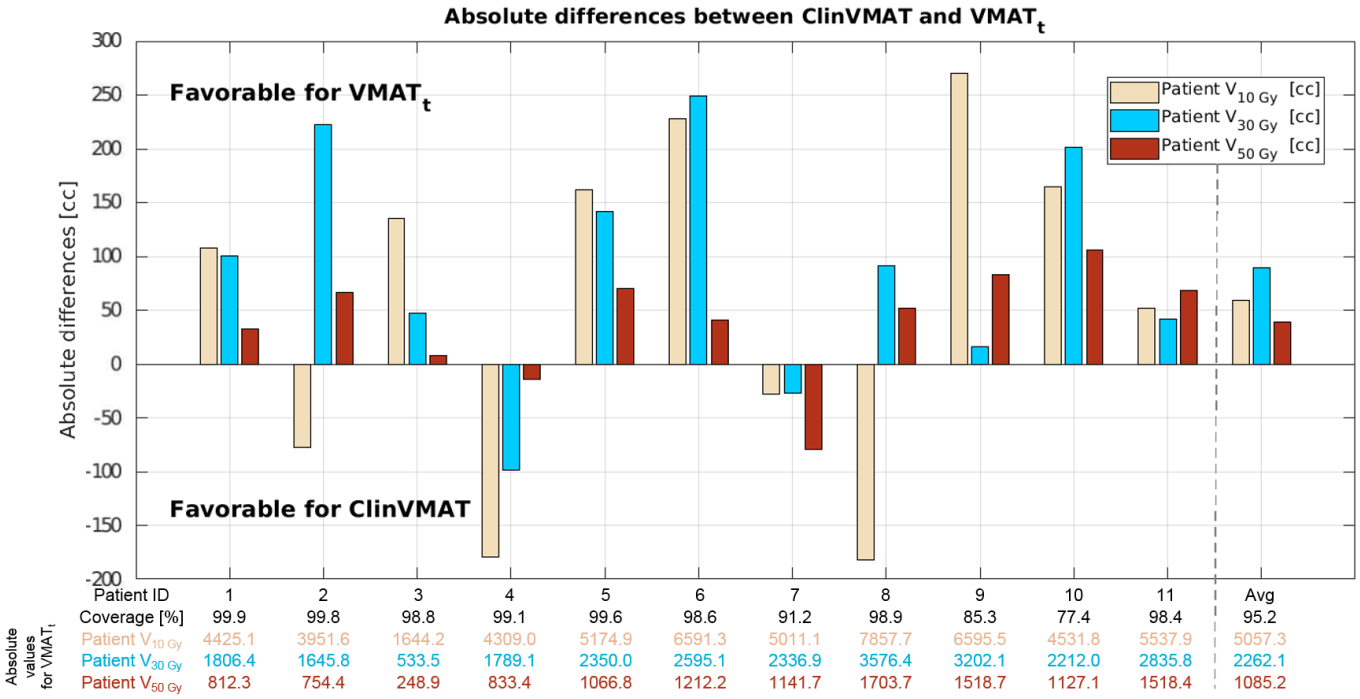
Patient ID	1	2	3	4	5	6	7	8	9	10	11	Avg
Coverage [%]	99.9	99.8	98.8	99.1	99.6	98.6	91.2	98.9	85.3	77.4	98.4	95.2
Absolute values for VMAT$_t$												
Cochlea$_R$	40.7	33.9	20.3	33.8	36.8	17.6	55.1	33.8	44.8	44.8	45.5	37.0
Cochlea$_L$	34.2	37.3	36.8	32.8	34.9	33.5	35.9	34.8	54.1	44.2	47.0	38.7
Esophagus	12.2	23.0	0.2	30.1	12.9	27.4	37.9	31.3	24.7	35.6	22.8	23.5
Superior SwM	66.0	62.7	55.6	68.7	60.2	56.4	69.8	61.4	69.9	69.5	70.0	64.6
Middle SwM	57.3	50.4	24.4	45.9	41.3	38.5	48.2	52.9	62.4	64.9	70.0	50.6
Inferior SwM	22.0	28.1	1.6	22.3	22.8	26.7	20.4	41.9	34.6	48.9	55.2	29.5

(c)



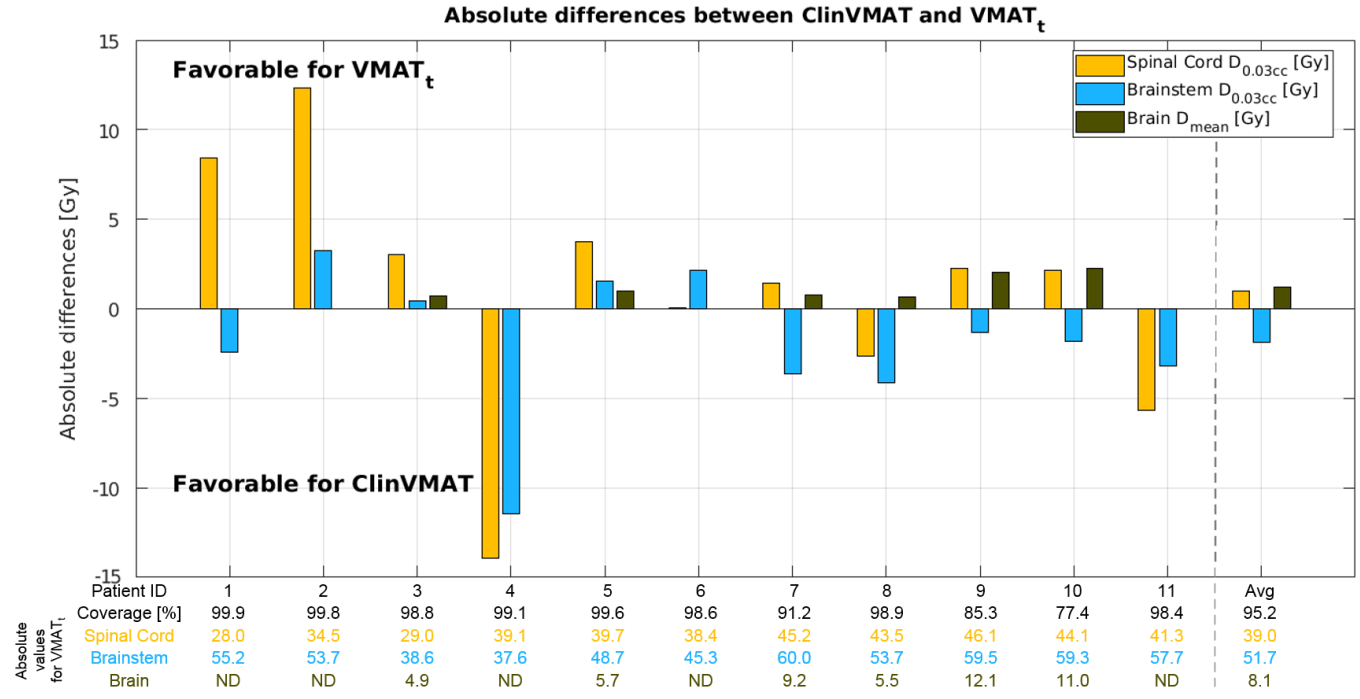
Patient ID	1	2	3	4	5	6	7	8	9	10	11	Avg
Coverage [%]	99.9	99.8	98.8	99.1	99.6	98.6	91.2	98.9	85.3	77.4	98.4	95.2
Absolute values for VMAT$_t$												
Mandible	62.9	52.1	72.0	72.9	72.4	72.6	71.2	72.2	70.6	71.0	71.2	69.2
Oral Cavity	36.4	35.9	31.0	42.8	40.9	37.3	48.9	33.2	46.0	36.4	42.8	39.2
Lens$_R$	2.0	ND	0.8	6.2	3.0	6.7	7.2	2.4	7.0	7.2	10.4	5.3
Lens$_L$	2.2	ND	0.8	3.9	2.8	7.7	6.8	3.2	6.9	6.9	4.8	4.6

(d)



Absolute values for VMAT$_t$	Patient ID	1	2	3	4	5	6	7	8	9	10	11	Avg
	Coverage [%]	99.9	99.8	98.8	99.1	99.6	98.6	91.2	98.9	85.3	77.4	98.4	95.2
	Patient V$_{10\,Gy}$	4425.1	3951.6	1644.2	4309.0	5174.9	6591.3	5011.1	7857.7	6595.5	4531.8	5537.9	5057.3
	Patient V$_{30\,Gy}$	1806.4	1645.8	533.5	1789.1	2350.0	2595.1	2336.9	3576.4	3202.1	2212.0	2835.8	2262.1
	Patient V$_{50\,Gy}$	812.3	754.4	248.9	833.4	1066.8	1212.2	1141.7	1703.7	1518.7	1127.1	1518.4	1085.2

(e)



Absolute values for VMAT$_t$	Patient ID	1	2	3	4	5	6	7	8	9	10	11	Avg
	Coverage [%]	99.9	99.8	98.8	99.1	99.6	98.6	91.2	98.9	85.3	77.4	98.4	95.2
	Spinal Cord	28.0	34.5	29.0	39.1	39.7	38.4	45.2	43.5	46.1	44.1	41.3	39.0
	Brainstem	55.2	53.7	38.6	37.6	48.7	45.3	60.0	53.7	59.5	59.3	57.7	51.7
	Brain	ND	ND	4.9	ND	5.7	ND	9.2	5.5	12.1	11.0	ND	8.1

(f)

Figure A.1: Differences between manually generated and clinically applied VMAT plans (ClinVMAT) and automatically generated VMAT (VMAT$_t$) plans for a) PTV70 coverage ($V_{95\%}$), hotspots ($V_{107\%}$) and CI for 66.5 Gy, b) parotids D_{mean}, submandibular glands D_{mean}, larynx D_{mean}, b) cochleas D_{mean}, esophagus D_{mean}, superior, middle and inferior swallowing muscles D_{mean}, d) mandible $D_{0.03\,cc}$, oral cavity D_{mean} and lenses D_{mean}, patient $V_{10\,Gy}$, $V_{30\,Gy}$ and $V_{50\,Gy}$, and f) spinal cord $D_{0.03\,cc}$, brainstem $D_{0.03\,cc}$ and brain D_{mean}. OARs presented by priority (from parotids to lenses) and for evaluated constraints (spinal cord, brainstem and brain). Positive is favorable for VMAT$_t$; negative is favorable for ClinVMAT. Below each patient ID is the coverage for which the plans were rescaled. * points at statistically significant differences with VMAT. ND=Non delineated OAR. For the brain it was not to possible to calculate statistical significance as the sample size was too small [12]. Patients ordered by increasing volume, as in figure 3.1.

B Dosimetric differences between generated plans for nasopharyngeal carcinoma

Table B.1: Comparison of dosimetric plan parameters for VMAT and differences to VMAT+1, VMAT+2 and VMAT+3, for nasopharyngeal carcinoma. Mean values, standard deviations (StD) and ranges refer to 10 patients (patients 1-6 and 8-11, see figure3.1), based on plans rescaled to the lowest coverage, for each patient. The first data column reports the results obtained with the VMAT. Statistically non-significant (NS) for p-value > 0.05. For the brain it was not to possible to calculate statistical significance as the sample size was too small [12].

	VMAT		VMAT - VMAT1			VMAT - VMAT2		
	Mean ± StD	**[Min, Max]**	**Mean ± StD**	**[Min, Max]**	**p - value**	**Mean ± StD**	**[Min, Max]**	**p - value**
PTV70								
$V_{95\%}$ [%]	93.8 ± 12.1	[64.7, 99.8]	0 ± 0.1	[-0.1, 0.1]	NS	0 ± 0.1	[-0.1, 0.2]	NS
$V_{107\%}$ [cc]	1.3 ± 2.2	[0, 7]	0.1 ± 0.2	[-0.2, 0.7]	NS	0.2 ± 0.5	[-0.4, 1.3]	NS
CI	1.1 ± 0.2	[0.7, 1.2]	0 ± 0	[0, 0]	NS	0 ± 0	[0, 0]	NS
$Parotid_R$								
D_{mean} [Gy]	**32 ± 13.6**	[12.7, 53.2]	**1 ± 0.7**	[0.1, 2.4]	0.002	**1.8 ± 1.1**	[0.7, 4.3]	0.002
$Parotid_L$								
D_{mean} [Gy]	**40.2± 12.7**	[25, 59]	**1 ± 1**	[0.1, 2.8]	0.002	**1.6 ± 1.3**	[0.7, 4.6]	0.002
SMG_R								
D_{mean} [Gy]	52.1 ± 13.8	[35.2, 68.8]	0.2 ± 0.5	[-0.1, 1.4]	NS	0.2 ± 0.8	[-0.5, 2.2]	NS
SMG_L								
D_{mean} [Gy]	52.2 ± 13.6	[35.2, 69.9]	0.1 ± 0.2	[-0.2, 0.5]	NS	0.1 ± 0.4	[-0.7, 0.6]	NS
Larynx								
D_{mean} [Gy]	32.8 ± 8.3	[12.1, 43]	0.1 ± 0.9	[-1.7, 1.4]	NS	-0.1 ± 0.8	[-1.6, 1.3]	NS
$Cochlea_R$								
D_{mean} [Gy]	38.5 ± 12.8	[20, 55.7]	-1 ± 4.7	[-14.3, 2.5]	NS	-0.7 ± 5	[-14.3, 4.4]	NS
$Cochlea_L$								
D_{mean} [Gy]	41.8 ± 11.2	[34.7, 60.6]	0 ± 0.1	[-0.1, 0.4]	NS	0.1 ± 0.2	[-0.1, 0.5]	NS
Esophagus								
D_{mean} [Gy]	24.5 ± 11.3	[0, 35.5]	1.4 ± 2.5	[-0.6, 8]	0.039	0.9 ± 2.8	[-3.8, 7.3]	NS
Superior SwM								
D_{mean} [Gy]	62.6 ± 5.3	[53.3, 70.8]	0.1 ± 0.3	[-0.5, 0.6]	NS	0.1 ± 0.4	[-0.5, 0.7]	NS
Middle SwM								
D_{mean} [Gy]	49.9 ± 12.6	[25.3, 70.8]	0.1 ± 0.4	[-0.4, 0.9]	NS	-0.1 ± 0.7	[-1.6, 0.5]	NS
Inferior SwM								
D_{mean} [Gy]	31.8 ± 14.7	[2.6, 55.8]	-0.1 ± 0.9	[-2.5, 0.6]	NS	-0.2 ± 1	[-2.2, 1]	NS
Mandible								
$D_{0.03\ cc}$ [Gy]	67.7 ± 5.9	[53.9, 70.9]	0.3 ± 0.8	[-0.2, 2.7]	NS	0.2 ± 0.7	[-0.5, 2]	NS
Oral Cavity								
D_{mean} [Gy]	39.8 ± 4.6	[32, 48.5]	0 ± 1.4	[-2.5, 2.2]	NS	0.2 ± 2.4	[-3.6, 5.4]	NS
$Lens_R$								
$D_{0.03\ cc}$ [Gy]	6.4 ± 3.6	[0.6, 11.4]	0.2 ± 0.7	[-0.9, 1.5]	NS	-0.5 ± 1.7	[-3.1, 1.7]	NS
$Lens_L$								
$D_{0.03\ cc}$ [Gy]	6 ± 3.4	[0.8, 10.7]	0.4 ± 0.5	[0, 1.4]	0.004	0 ± 0.8	[-1.6, 0.7]	NS
Patient								
$V_{10\ Gy}$	**4999.5 ± 1686.6**	[1663.9, 7776.7]	**-117.9 ± 135.2**	[-309.7, 78.8]	0.037	**-181.4 ± 172.7**	[-474.6, 92.4]	0.01
$V_{30\ Gy}$	**2438 ± 899.3**	[566, 3840.5]	19.6 ± 39.9	[-33.4, 89.6]	NS	**35.4 ± 43.8**	[-40.2, 96.1]	0.037
$V_{50\ Gy}$	**1185.9 ± 470.8**	[258.8, 1874]	**11.3 ± 9.2**	[-1.7, 31.3]	0.004	**11.1 ± 11.4**	[-15.6, 22.6]	0.02
Spinal Cord								
$D_{0.03\ cc}$ [Gy]	42.3 ± 6.4	[29.3, 49.7]	1.7 ± 2.9	[-1.5, 7.1]	NS	1.3 ± 2.6	[-0.9, 6]	NS
Brainstem								
$D_{0.03\ cc}$ [Gy]	51.4 ± 8	[38, 59.4]	-0.6 ± 3.8	[-7.9, 5.2]	NS	-0.9 ± 3.4	[-7.8, 4.7]	NS
Brain								
D_{mean} [Gy]	8.5 ± 3.9	[5, 14]	-1.1 ± 0.9	[-2.5, 0.1]	NS	-2 ± 1.3	[-3.1, -0.1]	NS
$Optical\ Nerve_R$								
$D_{0.03\ cc}$ [Gy]	27 ± 20.8	[3.5, 54.4]	-0.4 ± 1.3	[-2.5, 1.8]	NS	-2.6 ± 3.3	[-9, 0.2]	NS
$Optical\ Nerve_L$								
$D_{0.03\ cc}$ [Gy]	**24.4 ± 20**	[2.4, 54.4]	-1.9 ± 5.5	[-15.5, 0.6]	NS	**-4.8 ± 6.7**	[-16, 0.3]	0.039
Chiasm								
$D_{0.03\ cc}$ [Gy]	22.7 ± 20.8	[3.8, 54.5]	-4 ± 8.7	[-25.2, 0.4]	NS	-7.9 ± 10.2	[-25.3, 0.3]	NS
$Retina_R$								
$D_{0.03\ cc}$ [Gy]	14.6 ± 12.7	[2.2, 39.1]	1 ± 1.3	[0, 3.4]	NS	-0.6 ± 2.6	[-4.5, 3]	NS
$Retina_L$								
$D_{0.03\ cc}$ [Gy]	16.2 ± 13.8	[1.6, 41.9]	0.3 ± 1.1	[-1.1, 2.2]	NS	-0.7 ± 4.1	[-7.9, 3.9]	NS

Table B.2: Comparison of dosimetric plan parameters for VMAT and differences to VMAT+3, VMAT+4 and VMAT+5, for nasopharyngeal carcinoma. Mean values, standard deviations (StD) and ranges refer to 10 patients (patients 1-6 and 8-11, see figure3.1). Data for VMAT is reported in table B.1. Statistically non-significant (NS) for p-value > 0.05. For the brain it was not to possible to calculate statistical significance as the sample size was too small [12].

	VMAT - VMAT3			VMAT - VMAT4			VMAT - VMAT5		
	Mean ± StD	**[Min, Max]**	**p - value**	**Mean ± StD**	**[Min, Max]**	**p - value**	**Mean ± StD**	**[Min, Max]**	**p - value**
PTV70									
$V_{95\%}$ [%]	0 ± 0.1	[-0.1, 0.1]	NS	0 ± 0	[0, 0]	NS	0 ± 0	[-0.1, 0]	NS
$V_{107\%}$ [cc]	0.3 ± 0.7	[-0.2, 1.7]	NS	0.4 ± 0.8	[-0.3, 2.4]	NS	0.4 ± 0.9	[-0.3, 2.3]	NS
CI	0 ± 0	[0, 0]	NS	0 ± 0	[0, 0]	NS	0 ± 0	[0, 0]	NS
$Parotid_R$									
D_{mean} [Gy]	**2.4 ± 1.4**	[0.9, 4.7]	0.002	**2.7 ± 1.6**	[0.9, 5.4]	0.002	**3 ± 1.7**	[0.9, 5.8]	0.002
$Parotid_L$									
D_{mean} [Gy]	**2 ± 1.4**	[0.8, 5]	0.002	**2.3 ± 1.5**	[0.8, 5.2]	0.002	**2.5 ± 1.5**	[1, 5.7]	0.002
SMG_R									
D_{mean} [Gy]	0.4 ± 1	[-0.3, 3]	NS	0.6 ± 1.2	[-0.3, 3.8]	NS	0.6 ± 1.3	[-0.1, 4]	NS
SMG_L									
D_{mean} [Gy]	0.2 ± 0.4	[-0.3, 0.9]	NS	**0.3 ± 0.3**	[-0.1, 0.8]	0.039	**0.4 ± 0.3**	[-0.2, 0.8]	0.02
Larynx									
D_{mean} [Gy]	-0.1 ± 0.9	[-1.7, 1.5]	NS	0 ± 1.1	[-1.5, 2]	NS	-0.3 ± 0.7	[-1.5, 0.7]	NS
$Cochlea_R$									
D_{mean} [Gy]	0 ± 5.4	[-14.4, 6.6]	NS	-0.5 ± 4.9	[-14.3, 2.5]	NS	-0.4 ± 5	[-14.3, 3.4]	NS
$Cochlea_L$									
D_{mean} [Gy]	**0.9 ± 1.5**	[-0.2, 4.4]	0.037	**0.9 ± 1.6**	[-0.2, 5.1]	0.027	**0.6 ± 1.1**	[-0.1, 3.6]	0.02
Esophagus									
D_{mean} [Gy]	1 ± 2.6	[-1.4, 7.6]	NS	1.3 ± 2.3	[-1.1, 7.1]	NS	1 ± 2.9	[-3, 7.5]	NS
Superior SwM									
D_{mean} [Gy]	0.3 ± 0.4	[-0.3, 0.9]	NS	**0.4 ± 0.5**	[-0.2, 1.2]	0.027	**0.5 ± 0.4**	[0.1, 1.4]	0.002
Middle SwM									
D_{mean} [Gy]	0 ± 0.6	[-1.2, 0.6]	NS	**0.3 ± 0.3**	[-0.3, 0.7]	0.037	**0.4 ± 0.4**	[-0.4, 1]	0.02
Inferior SwM									
D_{mean} [Gy]	-0.2 ± 1.1	[-2.2, 1.2]	NS	0 ± 1	[-1.9, 1.4]	NS	-0.2 ± 1.6	[-3.8, 1.4]	NS
Mandible									
$D_{0.03\ cc}$ [Gy]	0.3 ± 0.6	[-0.4, 1.8]	NS	0.3 ± 0.9	[-0.4, 2.9]	NS	0.1 ± 0.8	[-0.5, 2.2]	NS
Oral Cavity									
D_{mean} [Gy]	0.9 ± 2.6	[-2.7, 6.9]	NS	1.4 ± 2.7	[-1.4, 7.4]	NS	1.7 ± 2.9	[-0.8, 8.3]	NS
$Lens_R$									
$D_{0.03\ cc}$ [Gy]	-1.6 ± 2.4	[-5.8, 2.1]	NS	-1.3 ± 2.6	[-5.7, 2.6]	NS	-2 ± 3.2	[-6.5, 2.6]	NS
$Lens_L$									
$D_{0.03\ cc}$ [Gy]	-0.6 ± 2.8	[-7.7, 1.2]	NS	-0.6 ± 2.6	[-7.3, 0.7]	NS	-0.6 ± 2.4	[-6.4, 0.7]	NS
Patient									
$V_{10\ Gy}$	**-240.9 ± 192**	[-545.5, 33.4]	0.004	**-244.1 ± 210.6**	[-527.3, 27]	0.004	**-268.4 ± 229.2**	[-573.2, 32.9]	0.01
$V_{30\ Gy}$	**68.5 ± 58.1**	[2.4, 154.1]	0.002	**102.1 ± 70.9**	[8.2, 229.4]	0.002	**113.2 ± 73.5**	[-3.2, 242.2]	0.004
$V_{50\ Gy}$	**20.8 ± 15.2**	[-7.8, 39.1]	0.006	**28.4 ± 18**	[-0.8, 52]	0.004	**29.6 ± 21.8**	[-3, 54.7]	0.01
Spinal Cord									
$D_{0.03\ cc}$ [Gy]	1.3 ± 2.6	[-1.3, 6.3]	NS	1.7 ± 3.1	[-3, 7.5]	NS	**2.2 ± 2.5**	[-1.4, 6.5]	0.02
Brainstem									
$D_{0.03\ cc}$ [Gy]	0.2 ± 3.9	[-8, 6.7]	NS	1 ± 3.9	[-5.9, 9.3]	NS	1.4 ± 3.8	[-5.3, 9]	NS
Brain									
D_{mean} [Gy]	-2.4 ± 1.3	[-3.5, -0.4]	NS	-2.3 ± 1.3	[-3.7, -0.3]	NS	-2.4 ± 1.5	[-3.9, -0.2]	NS
$Optical\ Nerve_R$									
$D_{0.03\ cc}$ [Gy]	**-5.8 ± 5.7**	[-13.5, 0.3]	0.023	-7.3 ± 8	[-20.7, 0.4]	NS	**-7.5 ± 8.1**	[-20.9, 0.3]	0.023
$Optical\ Nerve_L$									
$D_{0.03\ cc}$ [Gy]	**-8.5 ± 7.8**	[-19.6, -0.1]	0.008	**-9.8 ± 9.4**	[-26.1, -0.1]	0.008	**-9.5 ± 9**	[-23.9, 0.1]	0.023
Chiasm									
$D_{0.03\ cc}$ [Gy]	**-8.4 ± 7.8**	[-19.9, 0]	0.008	**-9.6 ± 10.3**	[-26.5, 0.1]	0.023	**-10.1 ± 10.7**	[-28.5, 0.1]	0.039
$Retina_R$									
$D_{0.03\ cc}$ [Gy]	-3.4 ± 7.1	[-16.2, 3.5]	NS	-3.9 ± 5.8	[-13.7, 2.9]	NS	-3.9 ± 5	[-11.7, 1.9]	NS
$Retina_L$									
$D_{0.03\ cc}$ [Gy]	-1.8 ± 2.7	[-5.1, 2.1]	NS	-1.8 ± 2.3	[-4, 1.4]	NS	-3.2 ± 4.4	[-10.8, 1.5]	NS

C Mutual dosimetric comparisons for investigated beam configurations for nasopharyngeal carcinoma

PTV70 V95% (%)

Treatment A \ Treatment B	VMAT	VMAT+1	VMAT+2	VMAT+3	VMAT+4	VMAT+5
VMAT	93.7	0.002	0.02	$<-1e^{-4}$	$<-1e^{-4}$	$<-1e^{-4}$
VMAT+1	*	93.7	0.02	$<-1e^{-4}$	$<-1e^{-4}$	$<-1e^{-4}$
VMAT+2	*	*	93.7	$<-1e^{-4}$	$<-1e^{-4}$	$<-1e^{-4}$
VMAT+3	*	*	*	93.8	0.007	$<-1e^{-4}$
VMAT+4	*	*	*	*	93.7	$<-1e^{-4}$
VMAT+5	*	*	*	*	*	93.8

(a)

PTV70 V74.90 (%)

Treatment A \ Treatment B	VMAT	VMAT+1	VMAT+2	VMAT+3	VMAT+4	VMAT+5
VMAT	1.3	0.07	0.2	0.3	0.4	0.4
VMAT+1	*	1.3	0.1	0.2	0.4	0.4
VMAT+2	*	*	1.2	0.1	0.3	0.3
VMAT+3	*	*	*	1.0	0.1	0.1
VMAT+4	*	*	*	*	0.9	0.002
VMAT+5	*	*	*	*	*	0.9

(b)

Parotid$_R$ Dmean (Gy)

Treatment B

Treatment A	VMAT	VMAT+1	VMAT+2	VMAT+3	VMAT+4	VMAT+5
VMAT	32.1	1.0	1.8	2.4	2.7	3.0
VMAT+1	0.002	31.2	0.9	1.4	1.8	2.0
VMAT+2	0.002	0.002	30.3	0.5	0.9	1.1
VMAT+3	0.002	0.004	0.004	29.8	0.4	0.6
VMAT+4	0.002	0.004	0.004	0.004	29.4	0.2
VMAT+5	0.002	0.004	0.004	0.004	0.002	29.1

(c)

Parotid$_L$ Dmean (Gy)

Treatment B

Treatment A	VMAT	VMAT+1	VMAT+2	VMAT+3	VMAT+4	VMAT+5
VMAT	40.3	1.0	1.6	2.0	2.3	2.5
VMAT+1	0.002	39.3	0.6	1.0	1.2	1.5
VMAT+2	0.002	0.002	38.7	0.4	0.6	0.9
VMAT+3	0.002	0.002	0.002	38.3	0.2	0.5
VMAT+4	0.002	0.002	0.002	0.002	38.0	0.3
VMAT+5	0.002	0.002	0.002	0.002	0.002	37.8

(d)

SMG_R Dmean (Gy)

Treatment B

Treatment A	VMAT	VMAT+1	VMAT+2	VMAT+3	VMAT+4	VMAT+5
VMAT	52.2	0.2	0.2	0.4	0.6	0.6
VMAT+1	*	52.0	0.04	0.2	0.4	0.4
VMAT+2	*	*	51.9	0.2	0.3	0.4
VMAT+3	*	*	0.031	51.8	0.1	0.2
VMAT+4	*	*	0.039	0.039	51.6	0.06
VMAT+5	*	*	0.039	0.039	*	51.6

(e)

SMG_L Dmean (Gy)

Treatment B

Treatment A	VMAT	VMAT+1	VMAT+2	VMAT+3	VMAT+4	VMAT+5
VMAT	52.3	0.1	0.05	0.2	0.3	0.4
VMAT+1	*	52.2	-0.07	0.07	0.2	0.2
VMAT+2	*	*	52.2	0.1	0.2	0.3
VMAT+3	*	*	*	52.1	0.1	0.2
VMAT+4	0.039	0.012	0.004	*	52.0	0.06
VMAT+5	0.020	0.012	0.004	*	0.023	51.9

(f)

Larynx Dmean (Gy)

Treatment B

Treatment A	VMAT	VMAT+1	VMAT+2	VMAT+3	VMAT+4	VMAT+5
VMAT	32.9	0.05	-0.1	-0.1	0.05	-0.3
VMAT+1	*	32.8	-0.2	-0.2	-0.007	-0.4
VMAT+2	*	*	33.0	-0.04	0.2	-0.2
VMAT+3	*	*	*	33.0	0.2	-0.2
VMAT+4	*	*	*	*	32.8	-0.4
VMAT+5	*	0.027	*	*	*	33.2

(g)

Esophagus Dmean (Gy)

Treatment B

Treatment A	VMAT	VMAT+1	VMAT+2	VMAT+3	VMAT+4	VMAT+5
VMAT	24.6	1.4	0.9	1.0	1.3	1.0
VMAT+1	0.039	23.2	-0.5	-0.4	-0.09	-0.4
VMAT+2	*	*	23.7	0.2	0.5	0.1
VMAT+3	*	*	*	23.6	0.3	-0.04
VMAT+4	*	*	*	*	23.3	-0.3
VMAT+5	*	*	*	*	*	23.6

(h)

Cochlea$_R$ Dmean (Gy)

Treatment B

Treatment A	VMAT	VMAT+1	VMAT+2	VMAT+3	VMAT+4	VMAT+5
VMAT	38.6	-1.0	-0.7	0.02	-0.5	-0.4
VMAT+1	*	39.6	0.3	1.1	0.5	0.6
VMAT+2	*	*	39.3	0.7	0.2	0.3
VMAT+3	*	0.020	*	38.6	-0.5	-0.4
VMAT+4	*	*	*	*	39.1	0.1
VMAT+5	*	*	*	*	*	39.0

(i)

Cochlea$_L$ Dmean (Gy)

Treatment B

Treatment A	VMAT	VMAT+1	VMAT+2	VMAT+3	VMAT+4	VMAT+5
VMAT	41.9	0.03	0.1	0.9	0.9	0.6
VMAT+1	*	41.9	0.08	0.9	0.8	0.6
VMAT+2	*	*	41.8	0.8	0.8	0.5
VMAT+3	0.029	*	*	41.0	-0.06	-0.3
VMAT+4	0.027	0.037	0.049	*	41.0	-0.2
VMAT+5	0.020	0.037	0.027	*	*	41.3

(j)

Superior SwM Dmean (Gy)

Treatment A \ Treatment B	VMAT	VMAT+1	VMAT+2	VMAT+3	VMAT+4	VMAT+5
VMAT	62.7	0.1	0.1	0.3	0.4	0.5
VMAT+1	*	62.6	0.003	0.2	0.3	0.4
VMAT+2	*	*	62.6	0.2	0.3	0.4
VMAT+3	*	*	0.004	62.4	0.2	0.3
VMAT+4	0.027	0.010	0.004	0.006	62.3	0.1
VMAT+5	0.002	0.002	0.004	0.010	*	62.2

(k)

Middle SwM Dmean (Gy)

Treatment A \ Treatment B	VMAT	VMAT+1	VMAT+2	VMAT+3	VMAT+4	VMAT+5
VMAT	50.0	0.09	-0.1	-0.01	0.3	0.4
VMAT+1	*	49.9	-0.2	-0.1	0.2	0.3
VMAT+2	*	*	50.1	0.1	0.4	0.6
VMAT+3	*	*	*	50.0	0.3	0.4
VMAT+4	0.037	*	0.020	0.010	49.7	0.2
VMAT+5	0.020	0.049	0.049	0.037	*	49.6

(l)

Inferior SwM Dmean (Gy)

Treatment B

Treatment A

	VMAT	VMAT+1	VMAT+2	VMAT+3	VMAT+4	VMAT+5
VMAT	31.9	-0.1	-0.2	-0.2	-0.04	-0.2
VMAT+1	*	32.0	-0.03	-0.06	0.1	-0.05
VMAT+2	*	*	32.0	-0.03	0.1	-0.02
VMAT+3	*	*	*	32.1	0.2	0.01
VMAT+4	*	*	*	0.020	31.9	-0.1
VMAT+5	*	*	*	*	*	32.1

(m)

Mandible D0.03 cc (Gy)

Treatment B

Treatment A	VMAT	VMAT+1	VMAT+2	VMAT+3	VMAT+4	VMAT+5
VMAT	67.7	0.3	0.3	0.3	0.3	0.1
VMAT+1	*	67.4	-0.09	-0.06	-0.03	-0.2
VMAT+2	*	*	67.4	0.03	0.06	-0.1
VMAT+3	*	*	*	67.4	0.03	-0.2
VMAT+4	*	*	*	*	67.4	-0.2
VMAT+5	*	*	*	*	*	67.6

(n)

Oral Cavity Dmean (Gy)

Treatment B

Treatment A	VMAT	VMAT+1	VMAT+2	VMAT+3	VMAT+4	VMAT+5
VMAT	39.9	-0.05	0.2	0.9	1.4	1.7
VMAT+1	*	40.0	0.3	0.9	1.5	1.7
VMAT+2	*	*	39.7	0.7	1.2	1.5
VMAT+3	*	*	0.014	39.1	0.6	0.8
VMAT+4	*	0.006	0.006	0.010	38.5	0.2
VMAT+5	*	0.006	0.006	0.004	*	38.2

(o)

$Lens_R$ D0.03 cc (Gy)

Treatment B

Treatment A	VMAT	VMAT+1	VMAT+2	VMAT+3	VMAT+4	VMAT+5
VMAT	6.4	0.2	<-1e^{-4}	<-1e^{-4}	<-1e^{-4}	<-1e^{-4}
VMAT+1	*	6.2	<-1e^{-4}	<-1e^{-4}	<-1e^{-4}	<-1e^{-4}
VMAT+2	*	*	6.9	<-1e^{-4}	<-1e^{-4}	<-1e^{-4}
VMAT+3	*	*	*	7.9	0.3	<-1e^{-4}
VMAT+4	*	*	*	0.039	7.7	<-1e^{-4}
VMAT+5	*	*	*	*	*	8.4

(p)

$Lens_L$ D0.03 cc (Gy)

Treatment B

Treatment A	VMAT	VMAT+1	VMAT+2	VMAT+3	VMAT+4	VMAT+5
VMAT	6.0	0.4	<-1e^{-4}	<-1e^{-4}	<-1e^{-4}	<-1e^{-4}
VMAT+1	0.004	5.5	<-1e^{-4}	<-1e^{-4}	<-1e^{-4}	<-1e^{-4}
VMAT+2	*	*	6.0	<-1e^{-4}	<-1e^{-4}	<-1e^{-4}
VMAT+3	*	*	*	6.6	0.001	0.03
VMAT+4	*	*	*	*	6.6	0.03
VMAT+5	*	*	*	*	*	6.6

(q)

Patient V10 Gy (cc)

Treatment A \ Treatment B	VMAT	VMAT+1	VMAT+2	VMAT+3	VMAT+4	VMAT+5
VMAT	4999.9	-117.9	-181.4	-240.7	-244.1	-268.3
VMAT+1	0.037	5117.8	-63.5	-122.8	-126.1	-150.3
VMAT+2	0.010	*	5181.3	-59.3	-62.7	-86.9
VMAT+3	0.004	0.010	*	5240.6	-3.4	-27.6
VMAT+4	0.004	0.006	*	*	5244.0	-24.2
VMAT+5	0.010	0.006	0.027	*	*	5268.2

(r)

Patient V30 Gy (cc)

Treatment A \ Treatment B	VMAT	VMAT+1	VMAT+2	VMAT+3	VMAT+4	VMAT+5
VMAT	2438.2	19.4	35.3	67.8	101.7	112.2
VMAT+1	*	2418.8	15.9	48.4	82.3	92.8
VMAT+2	0.037	*	2403.0	32.5	66.4	76.9
VMAT+3	0.002	0.014	0.027	2370.4	33.9	44.4
VMAT+4	0.002	0.002	0.004	0.010	2336.6	10.5
VMAT+5	0.004	0.004	0.004	0.006	0.027	2326.1

(s)

Patient V50 Gy (cc)

Treatment B

Treatment A

	VMAT	VMAT+1	VMAT+2	VMAT+3	VMAT+4	VMAT+5
VMAT	1186.1	11.2	11.2	20.6	28.4	29.6
VMAT+1	0.004	1174.9	-0.06	9.4	17.2	18.4
VMAT+2	0.020	*	1174.9	9.5	17.3	18.5
VMAT+3	0.006	0.014	0.002	1165.5	7.8	9.0
VMAT+4	0.004	0.002	0.002	0.002	1157.7	1.2
VMAT+5	0.010	0.014	0.010	0.027	*	1156.5

(t)

Spinal Cord D0.03 cc (Gy)

Treatment B

Treatment A

	VMAT	VMAT+1	VMAT+2	VMAT+3	VMAT+4	VMAT+5
VMAT	42.3	1.7	1.3	1.3	1.7	2.2
VMAT+1	*	40.6	-0.4	-0.4	-0.05	0.5
VMAT+2	*	*	41.0	0.004	0.4	0.9
VMAT+3	*	*	*	41.0	0.4	0.9
VMAT+4	*	*	*	*	40.6	0.5
VMAT+5	0.020	*	*	0.021	*	40.1

(u)

Brainstem D0.03 cc (Gy)

Treatment B

Treatment A	VMAT	VMAT+1	VMAT+2	VMAT+3	VMAT+4	VMAT+5
VMAT	51.4	-0.6	-0.9	0.2	1.0	1.4
VMAT+1	*	52.0	-0.3	0.8	1.6	2.0
VMAT+2	*	*	52.2	1.0	1.9	2.3
VMAT+3	*	*	0.039	51.2	0.9	1.2
VMAT+4	*	*	0.037	*	50.3	0.4
VMAT+5	*	*	0.004	0.020	*	50.0

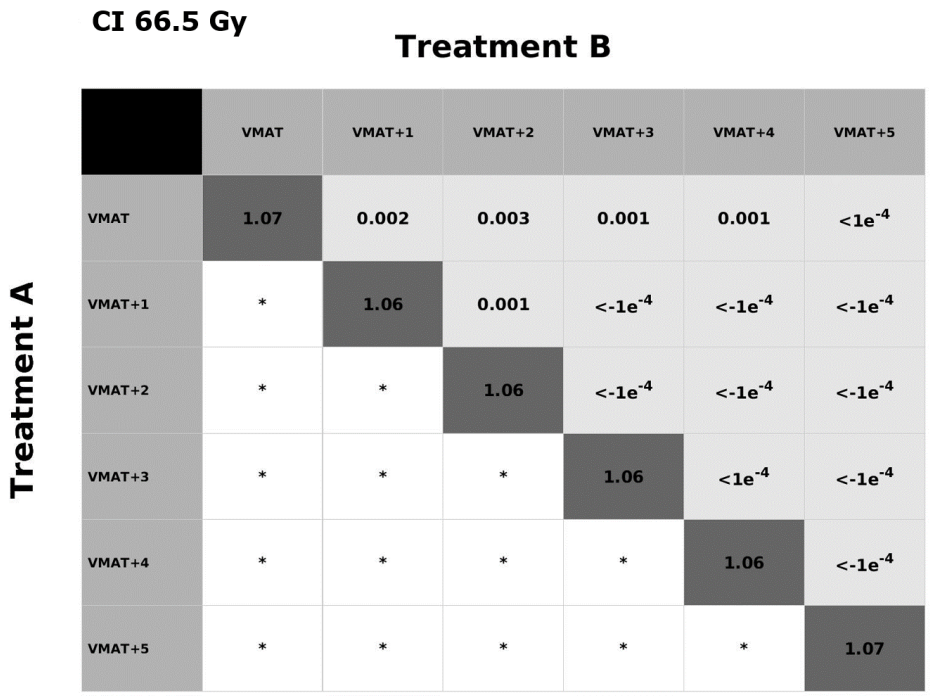
(v)

Brain Dmean (Gy)

Treatment B

Treatment A	VMAT	VMAT+1	VMAT+2	VMAT+3	VMAT+4	VMAT+5
VMAT	8.6	-1.1	-2.0	-2.4	-2.3	-2.4
VMAT+1		9.7	-1.0	-1.3	-1.2	-1.3
VMAT+2			10.7	-0.4	-0.3	-0.4
VMAT+3				11.0	0.1	0.002
VMAT+4					10.9	-0.1
VMAT+5						11.0

(w)



(x)

Figure C.1: Mutual dosimetric comparisons of all investigated beam configurations for NPC, based on plans rescaled to the lowest coverage for each patient. For the brain it was not to possible to calculate statistical significance as the sample size was too small [12]. Based on plans rescaled to the lowest coverage for each patient.

D Dosimetric differences between generated plans for mediastinal lymphoma

e D.1: Comparison of dosimetric plan parameters for VMAT and differences to VMAT+1, VMAT+2 and VMAT+3, for mediastinal lymphoma. Mean values, standard deviations (StD) and ranges refer to patients in the study. The first data column reports the results obtained with the VMAT. Based on plans rescaled to 99% PTV coverage ($V_{95\%} = 99\%$). Statistically non-significant (NS) for p-value > 0.05.

	VMAT		**VMAT - VMAT+1**			**VMAT - VMAT+2**			**VMAT - VMAT+3**		
	Mean ± StD	**[Min, Max]**	**Mean ± StD**	**[Min, Max]**	**p-value**	**Mean ± StD**	**[Min, Max]**	**p-value**	**Mean ± StD**	**[Min, Max]**	**p-value**
PTV											
$V_{95\%}$ [%]	99 ± 0	[98.9, 99.1]	0 ± 0	[-0.1, 0]	NS	0 ± 0	[-0.1, 0]	NS	0 ± 0	[0, 0]	NS
$V_{107\%}$ [%]	0.8 ± 0.5	[0.1, 1.9]	0 ± 0.2	[-0.3, 0.4]	NS	0 ± 0.2	[-0.2, 0.4]	NS	0 ± 0.2	[-0.5, 0.4]	NS
$V_{<90\%}$ [cc]	**0 ± 0.1**	[0, 0.2]	0 ± 0	[-0.1, 0]	NS	0 ± 0	[-0.1, 0]	NS	0 ± 0.1	[-0.2, 0]	NS
CI	**1.17 ± 0.1**	[1.1, 1.3]	**0.005 ± 0**	[0, 0.005]	< 0.001	**0.005 ± 0**	[0, 0.005]	< 0.001	**0.005 ± 0**	[0, 0.005]	< 0.001
Breasts											
D_{mean} [Gy]	**1.6 ± 1.3**	[0.2, 4.9]	0 ± 0.2	[-0.7, 0.2]	NS	0 ± 0.3	[-0.9, 0.4]	NS	**0.1 ± 0.3**	[-0.8, 0.6]	0.032
V_{4Gy} [%]	**7.9 ± 7.8**	[0, 30]	-0.1 ± 2	[-8.5, 2]	NS	-0.7 ± 3.3	[-12.7, 3.3]	NS	0.1 ± 2.9	[-10.9, 5.9]	NS
Heart											
D_{mean} [Gy]	**5.6 ± 5.8**	[0.3, 18.3]	**0.3 ± 0.4**	[-0.3, 1.1]	< 0.001	**0.6 ± 0.7**	[-0.2, 2.8]	< 0.001	**0.5 ± 0.5**	[0, 1.6]	< 0.001
Lungs											
D_{mean} [Gy]	**7.4 ± 3.2**	[2.1, 13.1]	**0.3 ± 0.2**	[0, 0.7]	< 0.001	**0.4 ± 0.3**	[0, 0.9]	< 0.001	**0.6 ± 0.4**	[0, 1.3]	< 0.001
V_{5Gy} [%]	**40.4 ± 16.9**	[9.1, 71.5]	**2.5 ± 2.4**	[-2.4, 8]	< 0.001	**3.5 ± 2.4**	[-0.2, 7.8]	< 0.001	**4.3 ± 3.3**	[-0.2, 12.9]	< 0.001
V_{20Gy} [%]	**13.8 ± 8.2**	[3.2, 28.3]	**0.3 ± 0.6**	[-1, 1.6]	0.001	**0.4 ± 0.7**	[-1.3, 2.1]	0.001	**0.7 ± 0.8**	[-0.6, 2.7]	< 0.001
Patient											
V_{5Gy} [cc]	**5010.3 ± 2424.1**	[1124.1, 10569.2]	**179.5 ± 164.5**	[-4.4, 547.9]	< 0.001	**227.2 ± 194.6**	[-61, 628.8]	< 0.001	**279.6 ± 239.7**	[49.3, 839.7]	< 0.001
V_{20Gy} [cc]	**1720.6 ± 994.5**	[304.1, 3924.7]	**26.4 ± 41.2**	[-24.9, 152.6]	0.001	**44.6 ± 55.8**	[-29.4, 184.7]	< 0.001	**54.8 ± 67**	[-128.9, 191.1]	< 0.001

Table D.2: Differences between VMAT and VMAT+4, VMAT+5 and FaB-VMAT. Mean values, standard deviations (StD) and ranges refer to the 25 patients in the study. Results obtained with VMAT in table. D.1. Statistically non-significant (NS) for p-value > 0.05.

	VMAT - VMAT+4			**VMAT - VMAT+5**			**VMAT - FaB-VMAT**		
	Mean $\pm$ StD	**[Min, Max]**	**p-value**	**Mean $\pm$ StD**	**[Min, Max]**	**p-value**	**Mean $\pm$ StD**	**[Min, Max]**	**p-value**
PTV									
$V_{95\%}$ [%]	0 ± 0	[-0.1, 0]	NS	0 ± 0	[-0.1, 0]	NS	0 ± 0	[-0.1, 0]	NS
$V_{107\%}$ [%]	0 ± 0.2	[-0.4, 0.4]	NS	0 ± 0.2	[-0.3, 0.4]	NS	0 ± 0.2	[-0.3, 0.4]	NS
$V_{<90\%}$ [cc]	**0.01 $\pm$ 0.01**	[-0.2, 0]	0.021	**0.01 $\pm$ 0.1**	[-0.3, 0]	0.015	0 ± 0.01	[-0.1, 0.1]	NS
CI	**0.01 $\pm$ 0**	[0, 0]	< 0.001	**0.02 $\pm$ 0**	[0, 0]	< 0.001	**0.01 $\pm$ 0**	[0, 0]	< 0.001
Breasts									
D_{mean} [Gy]	**0.1 $\pm$ 0.2**	[-0.3, 0.7]	0.005	**0.1 $\pm$ 0.2**	[-0.1, 1]	0.003	**0.2 $\pm$ 0.2**	[-0.1, 0.7]	< 0.001
V_{4Gy} [%]	0.6 ± 1.9	[-3.1, 5.9]	NS	0.8 ± 2	[-1.8, 7.8]	NS	**1.2 $\pm$ 1.8**	[-1, 4.9]	0.014
Heart									
D_{mean} [Gy]	**0.5 $\pm$ 0.5**	[0, 1.6]	< 0.001	**0.5 $\pm$ 0.4**	[0, 1.4]	< 0.001	**0.4 $\pm$ 0.4**	[-0.1, 1.5]	< 0.001
Lungs									
D_{mean} [Gy]	**0.6 $\pm$ 0.4**	[0, 1.4]	< 0.001	**0.6 $\pm$ 0.5**	[-0.1, 1.6]	< 0.001	**0.5 $\pm$ 0.4**	[-0.2, 1.2]	< 0.001
V_{5Gy} [%]	**4.5 $\pm$ 4**	[-2.6, 14]	< 0.001	**4.8 $\pm$ 4.1**	[-1.1, 15.2]	< 0.001	**3.8 $\pm$ 3.6**	[-2.3, 11.9]	< 0.001
V_{20Gy} [%]	**0.8 $\pm$ 0.8**	[-0.3, 2.8]	< 0.001	**0.9 $\pm$ 0.8**	[-0.7, 2.6]	< 0.001	**0.6 $\pm$ 0.6**	[-0.7, 1.8]	< 0.001
Patient									
V_{5Gy} [cc]	**297.5 $\pm$ 266**	[-30, 924.6]	< 0.001	**310.1 $\pm$ 288.4**	[-5.8, 1035.6]	< 0.001	**270.1 $\pm$ 218.3**	[18, 677]	< 0.001
V_{20Gy} [cc]	**65.5 $\pm$ 66.2**	[-98.1, 205.6]	< 0.001	**77 $\pm$ 73.8**	[-93.2, 222.7]	< 0.001	**62.9 $\pm$ 49.9**	[-30.3, 164]	< 0.001

E Mutual dosimetric comparisons for investigated beam configurations for mediastinal lymphoma

PTV V95% (%)

Treatment A \ Treatment B	VMAT	VMAT+1	VMAT+2	VMAT+3	VMAT+4	VMAT+5	FABVMAT
VMAT	99.0	-0.0	-0.0	-0.0	-0.0	-0.0	-0.0
VMAT+1	*	99.0	-0.0	-0.0	-0.0	-0.0	-0.0
VMAT+2	*	*	99.0	0.0	-0.0	-0.0	-0.0
VMAT+3	*	*	*	99.0	-0.0	-0.0	-0.0
VMAT+4	*	*	*	*	99.0	0.0	-0.0
VMAT+5	*	*	*	*	*	99.0	-0.0
FABVMAT	*	*	*	*	*	*	99.0

(a)

PTV V90% (cc)

Treatment A \ Treatment B	VMAT	VMAT+1	VMAT+2	VMAT+3	VMAT+4	VMAT+5	FABVMAT
VMAT	689.4	-0.0	0.0	0.0	0.0	0.0	-0.0
VMAT+1	*	689.5	0.0	0.0	0.1	0.0	0.0
VMAT+2	*	*	689.4	0.0	0.0	0.0	-0.0
VMAT+3	*	0.026	*	689.4	0.0	-0.0	-0.0
VMAT+4	*	0.037	*	*	689.4	-0.0	-0.0
VMAT+5	*	0.042	*	*	*	689.4	-0.0
FABVMAT	*	*	*	*	*	*	689.5

(b)

PTV V107% (%)

Treatment B

Treatment A

	VMAT	VMAT+1	VMAT+2	VMAT+3	VMAT+4	VMAT+5	FABVMAT
VMAT	0.0	-0.0	-0.0	-0.0	-0.0	-0.0	-0.0
VMAT+1	*	0.0	-0.0	-0.0	-0.0	-0.0	-0.0
VMAT+2	*	0.001	0.0	-0.0	-0.0	-0.0	0.0
VMAT+3	*	*	*	0.0	-0.0	-0.0	0.0
VMAT+4	0.039	0.018	*	*	0.1	-0.0	0.0
VMAT+5	0.037	0.004	*	*	*	0.1	0.0
FABVMAT	*	*	*	*	*	*	0.0

(c)

CI

Treatment B

Treatment A

	VMAT	VMAT+1	VMAT+2	VMAT+3	VMAT+4	VMAT+5	FABVMAT
VMAT	1.17	0.00	0.01	0.01	0.02	0.02	0.01
VMAT+1	0.004	1.17	0.00	0.01	0.01	0.02	0.01
VMAT+2	<0.001	0.020	1.17	0.00	0.01	0.01	0.01
VMAT+3	<0.001	<0.001	0.010	1.16	0.00	0.01	0.00
VMAT+4	<0.001	<0.001	<0.001	<0.001	1.16	0.00	-0.00
VMAT+5	<0.001	<0.001	<0.001	<0.001	*	1.15	-0.01
FABVMAT	<0.001	0.002	0.022	*	*	0.026	1.16

(d)

Breasts Dmean (Gy)

Treatment A \ Treatment B	VMAT	VMAT+1	VMAT+2	VMAT+3	VMAT+4	VMAT+5	FABVMAT
VMAT	1.7	0.0	-0.0	0.1	0.1	0.1	0.2
VMAT+1	*	1.7	-0.0	0.0	0.1	0.1	0.2
VMAT+2	*	*	1.8	0.1	0.1	0.2	0.2
VMAT+3	0.039	0.028	0.003	1.7	0.1	0.1	0.1
VMAT+4	0.006	0.010	0.002	*	1.6	0.0	0.1
VMAT+5	0.003	0.002	<0.001	0.029	*	1.6	0.0
FABVMAT	<0.001	<0.001	<0.001	0.012	*	*	1.5

(e)

Breasts V4Gy (%)

Treatment A \ Treatment B	VMAT	VMAT+1	VMAT+2	VMAT+3	VMAT+4	VMAT+5	FABVMAT
VMAT	9.4	-0.1	-0.8	0.1	0.8	1.0	1.4
VMAT+1	*	9.5	-0.6	0.3	0.9	1.1	1.5
VMAT+2	*	*	9.7	0.9	1.5	1.6	2.2
VMAT+3	*	*	*	8.8	0.6	0.8	1.3
VMAT+4	*	*	*	*	8.2	0.2	0.6
VMAT+5	*	0.034	*	*	*	8.0	0.4
FABVMAT	0.014	0.003	0.011	*	*	*	8.0

(f)

Heart Dmean (Gy)

Treatment A \ Treatment B	VMAT	VMAT+1	VMAT+2	VMAT+3	VMAT+4	VMAT+5	FABVMAT
VMAT	5.7	0.3	0.6	0.5	0.5	0.5	0.4
VMAT+1	<0.001	5.4	0.2	0.2	0.2	0.2	0.1
VMAT+2	<0.001	<0.001	5.1	-0.0	-0.0	-0.0	-0.2
VMAT+3	<0.001	<0.001	*	5.1	0.0	0.0	-0.1
VMAT+4	<0.001	<0.001	*	*	5.1	0.0	-0.1
VMAT+5	<0.001	<0.001	*	*	*	5.1	-0.2
FABVMAT	<0.001	*	*	0.038	*	0.014	5.3

(g)

Lungs Dmean (Gy)

Treatment A \ Treatment B	VMAT	VMAT+1	VMAT+2	VMAT+3	VMAT+4	VMAT+5	FABVMAT
VMAT	7.5	0.3	0.4	0.6	0.6	0.6	0.5
VMAT+1	<0.001	7.2	0.1	0.2	0.3	0.3	0.2
VMAT+2	<0.001	<0.001	7.1	0.1	0.2	0.2	0.0
VMAT+3	<0.001	<0.001	<0.001	7.0	0.0	0.1	-0.1
VMAT+4	<0.001	<0.001	<0.001	<0.001	7.0	0.0	-0.1
VMAT+5	<0.001	<0.001	<0.001	<0.001	0.006	6.9	-0.1
FABVMAT	<0.001	0.004	*	*	0.002	<0.001	7.1

(h)

Lungs V5Gy (%)

Treatment B

Treatment A	VMAT	VMAT+1	VMAT+2	VMAT+3	VMAT+4	VMAT+5	FABVMAT
VMAT	40.4	2.5	3.5	4.3	4.5	4.8	3.8
VMAT+1	<0.001	37.9	1.0	1.8	2.0	2.3	1.4
VMAT+2	<0.001	0.002	36.9	0.8	1.0	1.3	0.4
VMAT+3	<0.001	<0.001	0.005	36.1	0.2	0.5	-0.4
VMAT+4	<0.001	<0.001	0.007	*	35.9	0.3	-0.6
VMAT+5	<0.001	<0.001	0.008	0.011	0.036	35.7	-0.9
FABVMAT	<0.001	0.007	*	*	*	0.017	36.6

(i)

Lungs V20Gy (%)

Treatment B

Treatment A	VMAT	VMAT+1	VMAT+2	VMAT+3	VMAT+4	VMAT+5	FABVMAT
VMAT	13.8	0.3	0.4	0.7	0.8	0.9	0.6
VMAT+1	0.002	13.4	0.1	0.4	0.5	0.6	0.3
VMAT+2	0.001	*	13.3	0.3	0.4	0.4	0.1
VMAT+3	<0.001	0.002	0.004	13.1	0.1	0.2	-0.1
VMAT+4	<0.001	0.001	<0.001	0.013	13.0	0.1	-0.2
VMAT+5	<0.001	<0.001	<0.001	0.007	0.013	12.9	-0.3
FABVMAT	<0.001	0.012	*	*	0.038	0.042	13.2

(j)

Patient V5Gy (cc)

Treatment A \ Treatment B	VMAT	VMAT+1	VMAT+2	VMAT+3	VMAT+4	VMAT+5	FABVMAT
VMAT	5010.3	179.5	227.2	279.6	297.5	310.1	270.1
VMAT+1	<0.001	4830.8	47.8	100.2	118.0	130.7	90.6
VMAT+2	<0.001	0.014	4783.1	52.4	70.2	82.9	42.9
VMAT+3	<0.001	0.002	0.017	4730.7	17.8	30.5	-9.5
VMAT+4	<0.001	<0.001	0.005	*	4712.8	12.7	-27.3
VMAT+5	<0.001	<0.001	0.007	*	*	4700.2	-40.0
FABVMAT	<0.001	0.002	0.040	*	*	*	4740.2

(k)

Patient V20Gy (cc)

Treatment A \ Treatment B	VMAT	VMAT+1	VMAT+2	VMAT+3	VMAT+4	VMAT+5	FABVMAT
VMAT	1720.6	26.4	44.6	54.8	65.5	77.0	62.9
VMAT+1	0.001	1694.1	18.2	28.4	39.0	50.6	36.5
VMAT+2	<0.001	0.007	1675.9	10.2	20.8	32.3	18.2
VMAT+3	<0.001	0.001	0.020	1665.8	10.7	22.2	8.1
VMAT+4	<0.001	<0.001	0.011	0.011	1655.1	11.5	-2.6
VMAT+5	<0.001	<0.001	0.010	0.004	0.004	1643.6	-14.1
FABVMAT	<0.001	<0.001	0.030	*	*	*	1657.7

(l)

Figure E.1: Mutual dosimetric comparisons of all investigated beam configurations for ML, based on rescaled plans (PTV coverage = 99%). Based on plans rescaled to 99% PTV coverage ($V_{95\%} = 99\%$).